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Analysis of factors influencing early outcome following liver resection

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9. Wiggans MG, Shahtahmassebi G, Aroori S, Bowles MJ, Stell DA. (2014) Socioeconomic deprivation influences the likelihood of undergoing liver resection for colorectal liver metastases but not the outcome. *HPB (Oxford) 17:150–58.*

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Abstract

Analysis of factors influencing early outcome following liver resection

Matthew Wiggans

Introduction

The primary aim was to investigate factors associated with post-operative morbidity and mortality following liver resection. A secondary aim was to analyse the outcome of liver resection for colorectal liver metastases (CRLM) to identify factors associated with tumour recurrence and survival.

Methods

A retrospective review of a prospectively maintained database of patients undergoing liver resection between 2005 and 2012 was performed.

Results and Conclusions

Over a seven-year period 504 liver resections were performed. Liver resection for CRLM was performed less frequently among the most socioeconomically deprived population. However, socioeconomic deprivation was not associated with tumour recurrence (P=0.867). The major complication rate was 18.7% and was significantly associated with age, male gender, insulin-dependent diabetes, hypoalbuminaemia, synchronous bowel procedures, the extent of resection and requirement for blood transfusion.

The 90-day mortality rate was 2.7% in patients without post-hepatectomy liver failure or renal dysfunction, 20% in patients with single organ dysfunction and 45% in patients with both. Post-operative serum lactate predicted the 90-day mortality rate (28% when post-operative lactate ≥6mmol/L compared to 0.7% when lactate ≤2mmol/L). In the staging of patients with CRLM, the use of MRI in addition to CT showed no association with lower rates of post-operative intra-hepatic tumour recurrence (P=0.737) or disease-free survival (P=0.487). Recurrence rates were lower in patients when a fibrous tumour pseudocapsule was present (P=0.026). There was no association between tumour doubling time prior to surgery and post-operative survival. Change in tumour size after completion of chemotherapy is variable and sometimes rapid, especially in patients who initially respond to treatment. However, disease-free survival is determined by tumour behaviour during treatment and not by change in size after completion of chemotherapy.
Clinicians should consider multimodality imaging preoperatively, evaluate the role of preoperative MRI in the staging of colorectal liver metastases, and not use rate of growth of colorectal liver metastases as a predictor of poor outcome, Postoperative lactate should be used to guide level of postoperative care, and post hepatectomy liver failure in combination with renal dysfunction used to assess clinical progress. Histopathological reporting of the presence of pseudocapsules should be performed.

Contents

List of Tables

List of Figures

Definitions/Abbreviations

5FU – Fluorouracil

ASA – American Society of Anaesthesiologists

ATP – Adenosine triphosphate

BMI – Body mass index

CEA – Carcinoembryonic antigen

CLD – Chronic liver disease

CPEX – Cardiopulmonary exercise test

CR – Colorectal

CR – Complete response

CRLM – Colorectal liver metastases

CT – Computed tomography

CUSA – Cavitron Ultrasonic Surgical Aspirator

CVP – Central venous pressure

DT – Doubling time

EMVI – Extramural vascular invasion

ERCP – Endoscopic retrograde cholangiopancreatography

FNH – Focal nodular hyperplasia

GBC – Gallbladder carcinoma

GFR – Glomerular filtration rate

HCC – Hepatocellular carcinoma

HDU – High dependency unit

HPB – Hepatopancreatobiliary

IDDM – Insulin dependent diabetes

IHPBA – International Hepatopancreatobiliary Association

IMD – Index of multiple deprivation

INR – International normalised ratio

IOUS – Intraoperative ultrasound

IQR – Interquartile range

ISGLS – International Study Group of Liver Surgery

ITU – Intensive Care Unit

iu – International units

LDC – Liver directed chemotherapy

LNR – Lymph node ratio

LOS – Length of stay

MDT – Multidisciplinary team

Met - Metachronous

MR – Magnetic resonance

MRI – Magnetic Resonance Imaging

MUO – Metastases of unknown origin

NAFLD – Non-alcoholic fatty liver disease

NET – Neuroendocrine tumour

NIDDM – Non-insulin dependent diabetes

NL – Non-neoplastic liver

NLR – Neutrophil lymphocyte ratio

NPV – Negative predictive value

PC – Pseudocapsule

PD – Progressive disease

PE – Pulmonary embolus

PET – Positron Emission Tomography

PHLF – Post-hepatectomy liver failure

PHNT – Plymouth University Hospital

POD – Postoperative day

P-POSSUM - Portsmouth Physiologic and Operative Severity Score for the enUmeration of Mortality and morbidity

PPV – Positive predictive value

PR – Partial response

PT – Prothrombin time

RCPath – Royal College of Pathologists

REC – Research ethics committee

RECIST – Response Evaluation Criteria In Solid Tumours

RFA – Radiofrequency ablation

RIFLE - Risk, Injury, Failure, Loss, and End-stage kidney disease

SD – Stable disease

SES – Socioeconomic status

Syn – Synchronous

TN – Tumour necrosis

US – Ultrasound

+ve – Positive

-ve – Negative

Chapter 1 : Introduction

1.1 Background

1.1.1 History of liver resection

Documented evidence of the first liver resections dates from the late nineteenth century. During this period, surgeons feared operating on such a vascular organ due to the risk of catastrophic haemorrhage. Furthermore, the physiology of the liver and the effect of removing part of such a vital organ were poorly understood. It is therefore not surprising that the first resections were performed solely for trauma. In 1716, Berta[1] resected a protruding portion of liver following a self-inflicted stab wound and in 1870 Von Bruns successfully resected a lacerated portion of the liver caused by a gunshot wound during the Franco-Prussian war[2]. Following on from these early resections for trauma, the first reported resection of a solid liver tumour was performed by Linz in 1886[2] who removed a hepatic adenoma. Although this patient subsequently died from haemorrhage, the feasibility of resection had now been demonstrated and in 1888 Langenbuch recorded the first elective liver resection to remove a pedicled tumour from the left lobe[3]. He was subsequently followed by Tiffany in 1890[4] who removed a walnut-sized mass of biliary debris and calculi from the left lobe and Lucke in 1891 who removed the first malignant tumour[5]. Further resections were performed by Keen who reported resecting a bile duct adenoma in 1891 and an angioma in 1897. He also reported seventy five cases of liver resection performed around the world up until 1899[6] and performed the first true left lateral sectionectomy in the same year.

1.1.2 Anatomy

During these early liver resections there was very little understanding of the anatomy of the liver. Most surgeons believed that the liver was divided into right and left hemi-livers along the line of the falciform ligament[1]. However, around this time detailed anatomical studies of the liver were being performed by Cantlie and Rex which established it's lobar and segmental anatomy[7,8]. This aided liver surgery by allowing it to be performed in a more controlled manner with lower risk of haemorrhage. There was however significant variation in description of the liver, with some based on surface anatomy and others based on the internal features, particularly vascular and biliary anatomy.

The liver is the largest organ in the body and can be divided visually in its simplest form in to a right lobe and smaller left lobe by the falciform ligament which, runs from the liver to the umbilicus[9]. Postero-inferiorly the liver has an "H" shaped arrangement of fossae. Anteriorly and to the right lies the gall bladder fossa and to the left is the groove for the ligamentum teres. Posteriorly and to the right is the groove for the inferior vena cava and to the left is the fissure for the ligamentum venosum representing the obliterated fetal ductus venosus. The cross-bar of the "H" is the porta hepatis and this marks out the quadrate lobe anteriorly and caudate lobe posteriorly[9]. However, this classification does not take in to account the internal and functional anatomy of the liver and classifications reflecting this have supervened. For example, the quadrate lobe forms part of the right lobe but functionally it belongs to the left lobe[10]. Furthermore the caudate lobe has an independent blood supply and

venous drainage of the liver and is functionally separate to the right and left lobes[11].

At rest the liver receives a higher proportion of total cardiac output than any other organ (25%). It has a unique dual blood supply which is divided between the hepatic artery, contributing 25% to 30% of the blood supply, and the portal vein, which supplies 70% to 75%. Both blood supplies ultimately mix and then drain via the hepatic venous system[12]. Healey and Schroy were the first to divide the liver in to functional parts based upon hepatic artery branches and biliary ducts[13]. Further work was carried out by Goldsmith and Woodburne who developed a system of division based on the portal and hepatic veins[14]. Couinaud first suggested that the liver can be divided in to eight functionally independent segments based on the arrangement of portal and hepatic veins[15] and this work was extended by Bismuth who developed a new system based on a composite of the earlier descriptions of Goldsmith and Woodburne and Couinaud[16]. This divided the liver in to right and left hemilivers which could each be divided in to two sectors (right anteromedial, right posterolateral, left anterior and left posterior). Each right sector could be further divided in to two segments as could the left anterior sector. The left posterior sector formed a single segment and the caudate lobe was an independent segment.

In 1998 the International Hepato-Pancreato-Biliary Association sought to standardise the terminology of liver anatomy. This resulted in the Brisbane Terminology of hepatic anatomy and resections being adopted[17]. This consists of three orders of classification.

1. 1st Order – Separated by the midplane of the liver (plane that intersects the gallbladder fossa and the fossa for the inferior vena cava)
    - Right liver – segments 5-8 (+/- 1) – right hemihepatectomy
    - Left Liver – segments 2-4 (+/- 1) – left hemihepatectomy

2. 2nd Order – Separated by left intersectional plane between umbilical fissure and attachment of falciform ligament. No surface marking of right intersectional plane
    - Right anterior section – segments 5, 8 – Right anterior sectionectomy/sectorectomy
    - Right posterior section – segments 6, 7 – Right posterior sectionectomy/sectorectomy
    - Left medial section – segment 4 – Left medial sectionectomy/sectorectomy
    - Left lateral section – segments 2, 3 – Left lateral sectionectomy/sectorectomy
    - Right hemiliver plus left medial section – segments 4-8 (+/- 1) – Extended right hemihepatectomy/sectorectomy
    - Left hemiliver plus right anterior section – segments 2-5, 8 (+-1 1) – Extended left hemihepatectomy/sectorectomy

3. 3rd Order
    - Segments 1 – 8 – Segmentectomy
    - 2 Segments - Bisegmentectomy

1.1.3 Physiology

The liver has six broad functions:

1. Digestion

   Bile is secreted by hepatocytes and ductular epithelial cells. Bile consists of bile acids, cholesterol, lecithins, bile pigments which are end products of the breakdown of the haemoglobin in red blood cells, and an isotonic fluid with similar electrolyte concentrations to plasma containing sodium, potassium and chloride ions. Each day between 250-1500ml of bile enters the duodenum. The primary role of bile in digestion is the emulsification of lipids to permit digestion of lipids by lipases. The products of this digestion then form mixed micelles with bile acids which aid in the absorption of lipids and lipid-soluble molecules including the fat-soluble vitamins A, D E and K. Cholesterol is insoluble in water and bile provides the major route for its excretion[18].

2. Metabolism

   Carbohydrates, lipids and proteins are all metabolised by the liver. Insulin regulates blood glucose concentration by balancing peripheral glucose utilisation and hepatic glucose production[19]. Glucose enters hepatocytes via a plasma membrane transporter called GLUT2 and is used to synthesize glycogen[20].

   During the fasted state glycogenolysis occurs in the liver during which glycogen is hydrolysed by glycogen phosphorylase to produce glucose[21].

However, during prolonged fasting glycogen stores may become depleted. Gluconeogenesis allows the synthesis of glucose using lactate, pyruvate, glycerol, and amino acids. These substrates are either generated in the liver or transported from other tissues[21].

The role of the liver in lipid metabolism involves the uptake and degradation of chylomicron remnants. Hepatocytes also synthesise and secrete lipoproteins. The liver is the principle source of cholesterol in the body, and also its excretion via the secretion of bile[18].

The catabolism of proteins results in the production of ammonia which is converted to urea within the liver[18]. Urea is less toxic than ammonia and can be excreted easily in the urine. The remaining substances formed by the breakdown of amino acids can form the substrates for gluconeogenesis or be converted to Adenosine Triphosphate (ATP).

3. Detoxification

   The smooth endoplasmic reticulum of hepatocytes contains systems of enzymes and cofactors which are responsible for the transformation and excretion of many hormones, drugs and toxins[18]. This results in the inactivation of drugs and toxins and performs an important homeostatic role in the control of hormone levels. Conjugation of other compounds occurs with glucuronic acid, glycine or glutathione to make them water-soluble.

4. Storage

   In addition to the storage of glucose as glycogen the liver also stores fatty acids from the breakdown of triglycerides. It is also an important site of storage for iron, copper and vitamins A, D, E, K and B_{12}[18].

5. Synthesis

   As well as being involved in the synthesis of glucose and cholesterol and the breakdown of proteins, the liver also synthesises amino acids and proteins. These include the clotting factors I, II, V, VII, VIII, IX, X, XI and XII[22]. Protein C, Protein S and antithrombin are also synthesised in the liver which regulate anticoagulation[22]. The liver is also a site of thrombopoietin synthesis which regulates platelet production[23]. The liver is a major source of insulin-like growth factors and IGF binding proteins which have important endocrine activities relating to energy metabolism, body size, carcinogenesis, and various organ-specific functions[24].

6. Immunity

   The liver functions as a major part of the immune system. Kupffer cells in the liver are a critical component of the mononuclear phagocytic system. Due to the large volume of blood that passes through the hepatic portal system they play a pivotal role in both the hepatic and systemic response to pathogens[25].

1.1.4 Pathology of liver tumours

Primary liver malignancy includes one of the world's most common malignant neoplasms, hepatocellular carcinoma (HCC) as well as the less common cholangiocarcinoma and angiosarcoma[26].

Worldwide hepatocellular carcinoma is the fifth most common cancer in males and the seventh most common cancer in females, and is the third leading cause

of cancer-related death[27,28]. Risk factors for the development of HCC include hepatitis B and C infection[29] alcoholic cirrhosis and non-alcoholic fatty liver disease (NAFLD)[30]. Treatment of early stage HCC includes surgical resection +/- adjuvant chemotherapy, liver transplantation and locoregional therapy, whilst intermediate disease is often treated with transarterial chemoembolisation (TACE) and advanced disease may be treated with systemic therapy, cytotoxic chemotherapy, immunotherapy, or oncolytic virus therapy[31], or patients may receive palliative and best supportive care.

Cholangiocarcinoma is an epithelial cell malignancy which can arise from varying locations within the biliary tree. These can be classified by location as intrahepatic, perihilar, and distal cholangiocarcinoma[32]. Perihilar disease represents about half of all cases, distal disease 40%, and intrahepatic disease less than 10% of cholangiocarcinoma cases[33]. Mixed hepatocellular-cholangiocellular carcinomas have recently been acknowledged as a distinct subtype of cholangiocarcinoma[34]. In the majority no risk factor are identified for the development of cholangiocarcinoma but hepatitis B, C, cirrhosis and an association with primary sclerosing cholangitis have been identified[32]. Treatment includes cytotoxic therapies, liver resection and liver transplantation.

Angiosarcoma is a rare, aggressive tumour that grows into the lumen of pre-existing vascular spaces like sinusoids and terminal hepatic venules. Worldwide approximately 200 new cases are diagnosed annually and it is the most common primary malignant mesenchymal tumour of the liver in adults accounting for 2% of all primary hepatic malignancies[35]. There are few treatment guidelines, but liver resection may rarely be indicated for solitary tumours.

Benign liver lesions include haemangiomas, focal nodular hyperplasia and hepatocellular adenoma. Haemangiomas are the most common benign hepatic tumours and are often discovered incidentally[36]. Asymptomatic haemangiomas do not require surgical resection and the role of surgery is debatable even when symptomatic[37]. Focal nodular hyperplasia is the second most common benign liver tumour and is far more common in females (up to 90%) with an average age at presentation between 35 and 50 years[36]. Treatment is not recommended but if patients are symptomatic or imaging appearances are atypical surgery can be considered[36].

Hepatocellular adenomas have an even lower incidence and encompass various types of clonal benign hepatocellular proliferations[36] and are linked with the use of the oral contraceptive pill. However, they have the potential for both haemorrhage and malignant transformation and surgical resection has been recommended[38,39]. Guidelines suggest that the treatment of choice of adenomas in men is resection, but in women a period of six-month observation is recommended after lifestyle changes including weight loss and stopping the oral contraceptive pill[36].

Secondary malignancy of the liver accounts for 95% of all hepatic malignancies[40] and of these colorectal liver metastases (CRLM) are by far the most common[26]. Up until the 1980s patients with CRLM were often left untreated, but now they form the bulk of all resections performed.

Colorectal cancer is the third most common cause of cancer death and in the UK 39,000 new cases are diagnosed each year and over half of these develop liver metastases[41]. Globally it is estimated that 40-70% of patients with

colorectal cancer will develop CRLM[40]. Surgery provides a potential cure for these patients, but only 10-20% of patients with CRLM are considered suitable for resection.

1.1.5 Liver resection as a potential cure for malignant tumours

In terms of surgery offering a potential cure for malignant liver tumours the outcomes vary according to tumour type. Five year survival rates for patients undergoing liver resection for hepatocellular carcinoma have been reported between 34-91%[42–44].

In patients undergoing surgical resection for cholangiocarcinoma curative treatment with negative tumour margins can be achieved in less than 30% of patients[33]. The median survival time by of patients with lesions considered to be surgically resectable is 36 months[33,45].

Liver resection provides a potential cure for patients with colorectal liver metastases (CRLM), Five year survival rates currently range from 32% to 65%[40,41], a stark comparison to the five year survival rate of those without resection which approaches zero[40]. However surgery is not without risk and review of published studies suggests a 30 day mortality rate of 0-6.6% (median 2.8%)[41]. Untreated the prognosis for these patients is poor, with a median survival of less than nine months[46]. In patients with unresectable liver metastases survival has improved from 12 months in patients treated with fluorouracil therapy to approximately 2 years in those treated with combinations of oxaliplatin, fluorouracil and folinic acid (FOLFOX), capecitabine and oxaliplatin (CAPOX), or with irinotecan, folinic acid and fluorouracil (FOLFIRI)[47–50].

Published guidelines for the management of metastases of unknown origin (MUO) recommend a range of chemotherapy regimens[51], and surgery is rarely appropriate in the treatment of MUO due to the high rate of recurrence from the unknown primary.

1.1.6 Liver resections in the twentieth century

Advances in surgical technique as well as peri-operative care have led to a much wider application of liver resection. The first successful right sided lobectomy was performed by Wendell in 1911 [52], but the significance of this achievement and its relationship with segmental anatomy was not recognised until the work of Couinaud in 1954[53]. In 1949 a right hemihepatectomy was successfully performed by Honjo[54] in Japan and three years later the first true anatomic resection with vascular control was performed by Lortat-Jacob and Robert[55]. This anatomic resection paved the way for many other case reports of liver resection and this rise in the number of resections led to research into liver regeneration following resection. Regeneration of the liver was described in 1962 suggesting that complete regeneration could occur within three to six months of surgery[56].

During the following decades, the techniques of liver resection were modified and improved to improve patient safety. This included methods for anatomically-based segmental resections, the use of subcostal incisions rather than laparothoracotomies, the use of surgical drains, modern techniques for transecting the liver parenchyma, low central venous pressure anaesthesia[57] and improvements in postoperative support. However, there was a paucity of

large published series to support the widespread practice of liver resection. Instead there were numerous published single case reports often with few or no details of follow up. A review of published data in 1970 attempted to consolidate those case reports and small series to provide meaningful information regarding morbidity and mortality from liver resection. In these early reports in-hospital mortality following resection for primary liver carcinomas was observed to be 24% and 17% for metastatic liver tumours, with five year survival rates between 14% for primary liver carcinomas and 21% for metastases[58]. When compared to survival without treatment these results clearly suggested that liver resection offered a viable treatment option for such tumours.

1.1.7 Modern day liver resection techniques.

Whilst a better understanding of the anatomy and physiology of the liver has led to advances in liver resection surgeons still face the challenge of deciding upon anatomic, non-anatomic or wedge resections. The decision process must take in to account factors including tumour burden, risk of recurrence as well as the effect of preoperative chemotherapy and pre-existing liver disease as all of these factors can influence outcome after surgery[59].

1.1.7.1 Control of vascular inflow

Blood loss[60,61] and the requirement for blood transfusion[62,63] are associated with worse outcome after liver resection in terms of morbidity and mortality and blood transfusion has been associated with tumour recurrence[64,65]. Attempts that have been made to control vascular inflow include use of the Pringle manoeuvre[66], selective[67] and total hepatic vascular exclusion[68], total hepatic vascular exclusion with caval flow preservation[69], ischaemic pre-conditioning[70]

and use of the hanging manoeuvre[71] during hepatic mobilisation. A Cochrane review of these techniques concluded that intermittent vascular occlusion did not decrease morbidity after liver resection[72]. Among the different methods of vascular occlusion, intermittent portal triad clamping has most evidence to support the clinical application. Hepatic vascular exclusion was not recommended routinely. Ischaemic preconditioning before continuous portal triad clamping was felt to be of clinical benefit in reducing intensive therapy unit and hospital stay after liver resection.

1.1.7.2 Transection of liver parenchyma

In an attempt to reduce blood loss further various techniques for liver transection have been developed. These include: basic finger or clamp-fracturing (Kelly-Clasia) of parenchyma to expose vessels and biliary radicals, use of the Cavitron Ultrasound Surgical Aspirator (CUSA, Tyco Healthcare, Mansfield, MA, USA) which combines ultrasonic energy with aspiration to skeletonise these structures. Both the Harmonic Scalpel (Ethicon Endo-Surgery, Cincinnati, OH, USA) and the Ligasure Vessel Sealing System (Medtronic, Mansfield, MA, USA) are often used in laparoscopic liver resections but can also be used in open surgery to seal and divide vessels and biliary radicals[73,74]. Radiofrequency dissecting sealers (RFDS) link radiofrequency energy with cool saline to achieve blunt parenchymal dissection and haemostatic sealing of small vessels[75] and water jet dissection uses a high-pressure water jet to isolate vessels and biliary radicals which are then ligated[76]. Vascular surgical staplers have also been employed to quickly transect the liver parenchyma[77]. The use of these methods was also the subject of a Cochrane review which concluded that the clamp-crush technique is advocated as the

method of choice in liver parenchymal transection because it avoided special equipment, whereas the newer methods did not offer any benefit in decreasing the morbidity or transfusion requirement[78]. Furthermore the most recent Cochrane review in 2016 suggested that using special equipment for liver resection is not of any benefit in decreasing the mortality, morbidity, or blood transfusion requirements[79]. Importantly this review recommended the use of a radiofrequency dissecting sealer only in the clinical trial setting since there was low-quality evidence for increased harm without any evidence of benefits.

1.1.7.3 Laparoscopic liver surgery

Early attempts at laparoscopic liver surgery were in the 1990s and mainly involved laparoscopic wedge resections[80]. More recently major resections including hemihepatectomies are performed laparoscopically[81]. A recent meta-analysis[82] concluded that blood loss was lower, need for transfusion, pulmonary and cardiac complications, PHLF was less as was length of stay in those undergoing laparoscopic surgery. However, none of the studies included were randomised controlled trials and there was significant heterogeneity between patient groups making comparisons difficult. The results of a randomised controlled trial compared laparoscopic versus open liver resection for colorectal liver metastases demonstrated a lower rate of postoperative complication and length of stay but no difference in blood loss, operative time, mortality or positive resection margins[83].

1.1.7.4 Radio- and microwave- ablation of liver tumours

Radiofrequency ablation (RFA) is a minimally invasive treatment which uses heat to destroy cancer cells. A needle electrode is passed into the tumour under

image guidance either percutaneously or intra-operatively. High-frequency electrical currents are then passed through the tumour creating frictional heat produced by the ionic agitation of particles within the tumour that destroys the cancer cells surrounding the electrode[84]. Microwave ablation (MWA) uses microwaves to heat and destroy the tumour and is used for the same indications as RFA[85]. The procedure is less invasive than surgery and can be used to treat multiple lesions and can be repeated if necessary as tumours recur. In the liver, RFA and MWA are most commonly used to treat hepatocellular carcinoma[84] and colorectal liver metastases[86]. They are more effective at treating smaller tumours due to the risk of thermal damage to surrounding structures and limitations of the burn zone size. A recent randomised controlled trial has shown no difference in efficacy between the two techniques[87]. Ablation may be an alternative to resection in patients deemed not fit enough for surgery[88], in those with multilobar tumours that cannot be removed surgically and in those with impaired liver function[86,89]. It may also be used as an adjunct to surgical resection either as a separate procedure or performed intraoperatively[86].

1.1.8 Oncosurgery and colorectal liver metastases

The primary aim of tumour resection is to remove the tumour with an uninvolved margin (R0 resection)[90]. Without neoadjuvant chemotherapy however surgical resection is not possible in 70%–90% of patients with liver metastases from CRC due to excessive tumour burden. Neoadjuvant chemotherapy with either oxaliplatin or irinotecan based regimes can lead to down-sizing of tumour nodules leading to improved resectability[91].

First line chemotherapy with doublet (two chemotherapy agents) or triplet regimens (three agents) for a minimum of four courses is also used in patients with potentially resectable disease. In such patients neoadjuvant chemotherapy is associated with improved progression-free survival in patients with synchronous metastases[92]. In patients with metachronous disease the benefits of neoadjuvant chemotherapy are less clear[93]. Although the proportion of patients with CRLM who respond to liver directed chemotherapy (LDC) has been defined in many studies[92,94] the duration over which the changes are sustained following completion of treatment has not been described, and the consequences of tumour progression in the interval between completion of chemotherapy and surgery are unknown. This issue is addressed in greater detail in Chapter 5.

1.1.9 Liver resection within the South West Peninsula

The Peninsula Hepato-Pancreatico-Biliary (HPB) multidisciplinary team (MDT) was founded in July 2005. It was set up to serve the population of the South West Peninsula (1.8 million) and receives referrals from five hospitals: Royal Cornwall, University Hospital Plymouth (PHNT), Royal Devon and Exeter, Torbay and North Devon District Hospitals. The MDT meets weekly and is attended by radiologists, oncologists, surgeons and physicians. The MDT pathway for the assessment and treatment of colorectal liver metastases is shown below.

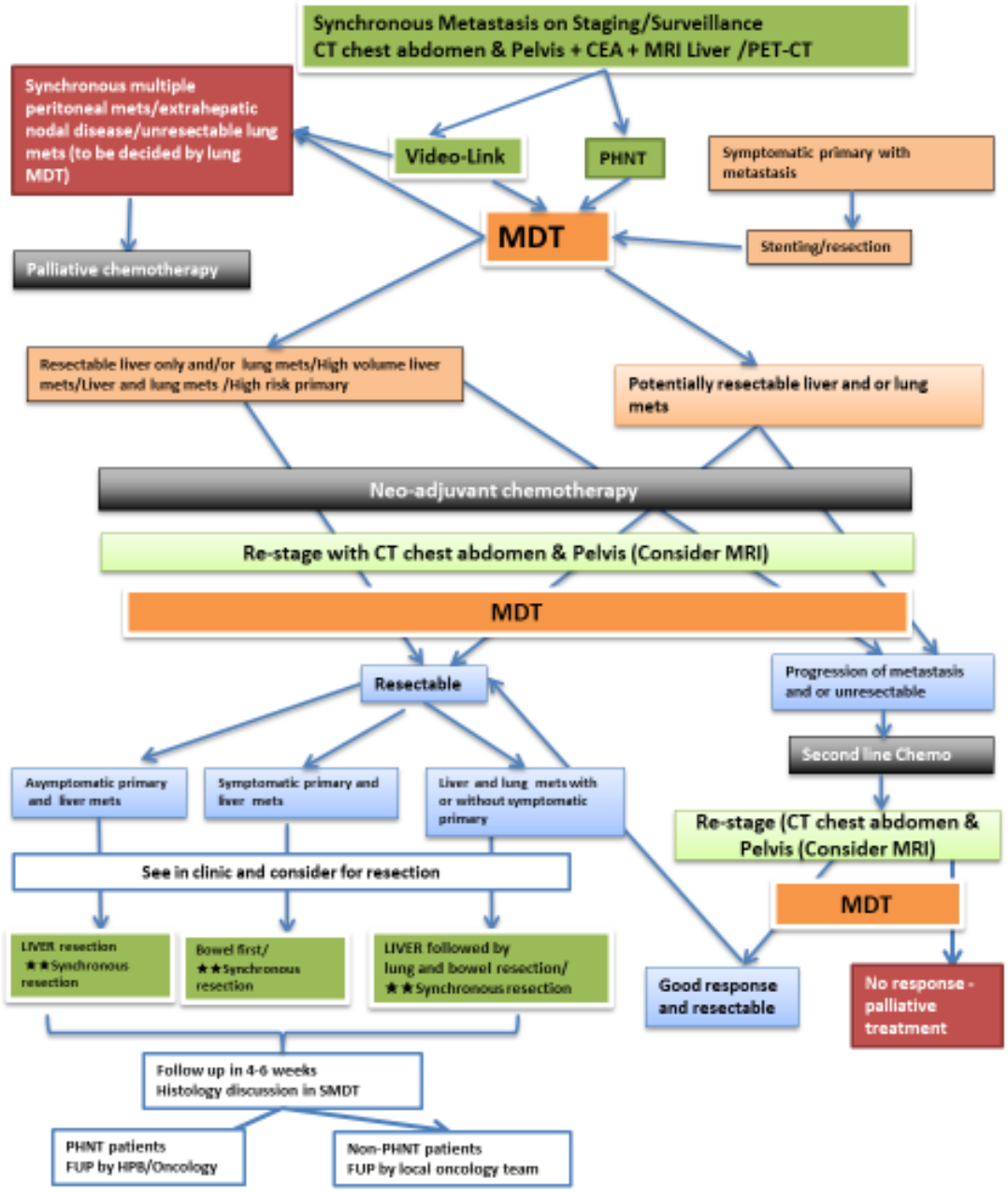
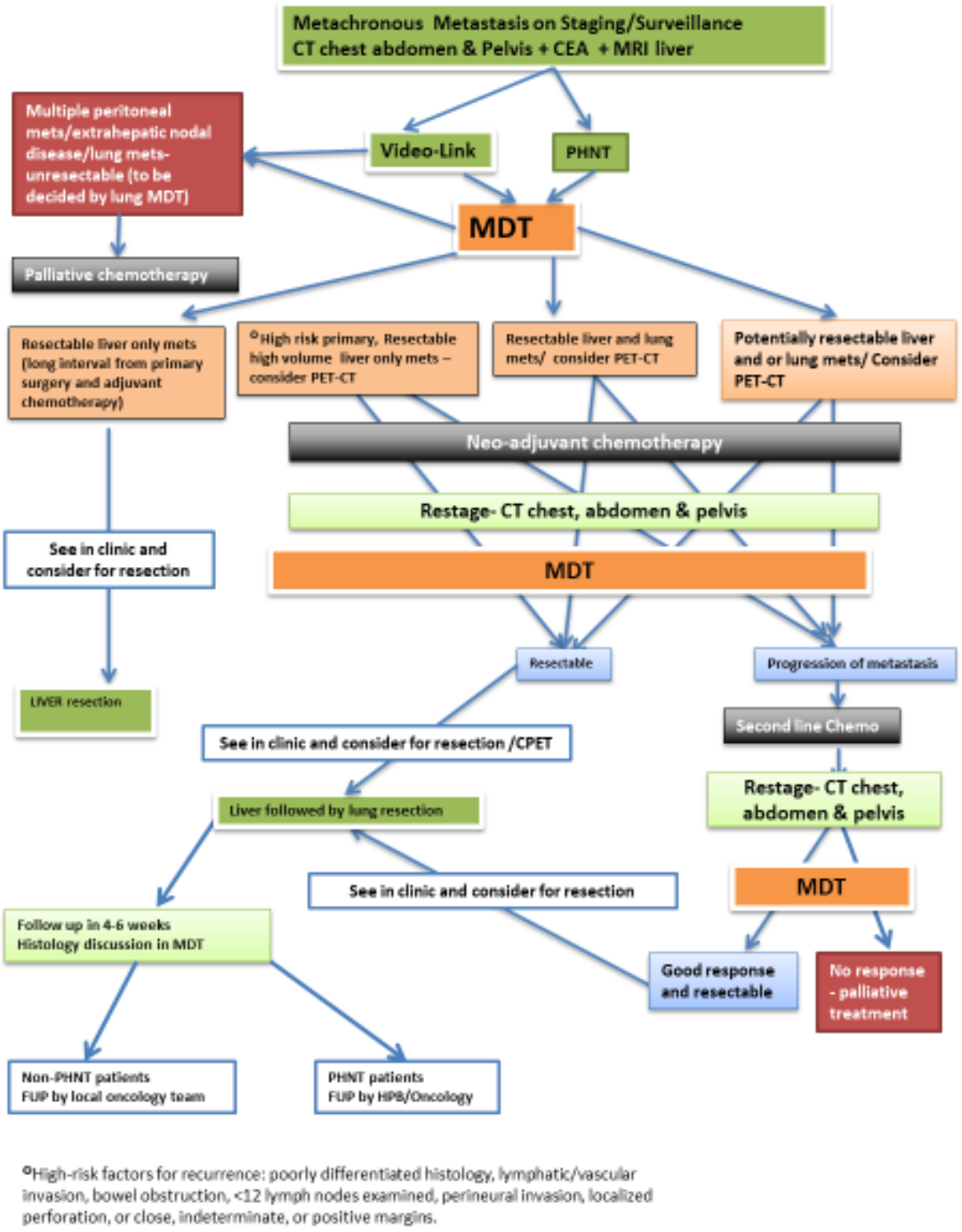


Figure 1.1 MDT pathway for patients with colonic cancer and synchronous liver metastases.



°High-risk factors for recurrence: poorly differentiated histology, lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, indeterminate, or positive margins.

Figure 1.2 MDT pathway for patients with colorectal cancer and metachronous liver metastases.

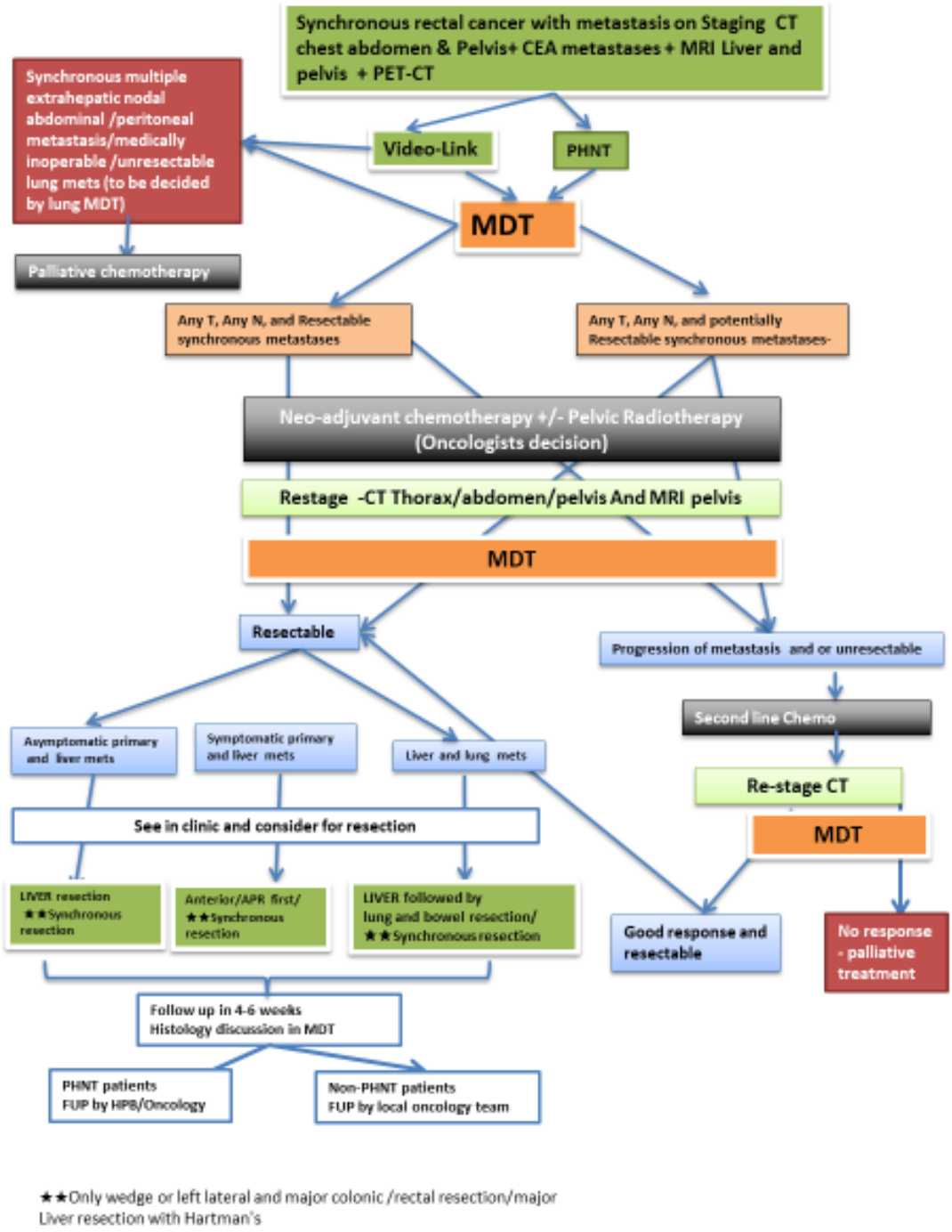


Figure 1.3 MDT pathway for patients with rectal cancer and synchronous liver metastases.

1.1.10 Preoperative imaging of colorectal liver metastases

Cancer staging is a method for describing the location, size and extent of spread of malignant tumours. This is used to facilitate the planning of treatment. Prior to liver resection for CRLM most patients undergo imaging of the thorax, abdomen and pelvis by CT scan. Modern helical CT scans have a per-lesion sensitivity and specificity of 51.8-84.6% and 77.2-98.0%. However, MRI scans have been recommended in pre-operative staging[95,96] due to their greater sensitivity and specificity (86.9-100% and 80.2-98.0%) particularly for the detection of sub-centimetre lesions[97,98] which may lead to a lower rate of intrahepatic recurrence after resection. Intraoperative ultrasound is also widely used for the detection of CRLM[99] but it is operator dependent and accurate figures for sensitivity and specificity are difficult to obtain and direct comparison with preoperative imaging is difficult to perform. However figures of 84.3% and 76.5% respectively have been reported[100]. This issue is addressed in greater detail in Chapter 3.

1.1.11 Tumour kinetics and doubling time

The growth rate of tumours provides an indication of the proportion of viable tumour cells and their proliferation rate. The growth rate therefore potentially gives an indication of tumour behaviour and responsiveness, as radiation and drug effectiveness are both strongly influenced by kinetic parameters[101]. Tumour growth rate is also an important indicator of prognosis[102–106]. The growth rate can be assessed by sequential measurement of

tumour size and is commonly expressed as the tumour doubling time (DT). Tumour DT can be calculated using the equation:

$$DT=Ti \times Log2 / (3 \times Log(Dp/Dr)$$

where Ti = time interval between radiological diagnosis and surgery, Dp = diameter at pathology and Dr = diameter at radiological diagnosis [107]

Although the survival of patients with untreated metastatic colorectal cancer has been described[108] the rate of growth of untreated colorectal liver metastases (CRLM) is not well defined, and little information is available regarding the influence of the pre-operative rate of growth of CRLM on survival following liver resection. This issue is addressed in greater detail in Chapter 4.

1.1.12 Obesity, diabetes, steatosis and liver surgery

Obesity, diabetes and hepatic steatosis often coexist in the metabolic syndrome[109]. Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of liver disease in Western countries[110]. It has been suggested that hepatic steatosis is associated with increased risk of postoperative complications after liver resection[111]. and both diabetes and obesity have been shown to be independent risk factors for postoperative complications following major surgery at other sites[112,113]. This issue is addressed in greater detail in Chapter 6.

1.1.13 Anaerobic metabolism and liver surgery

Lactic acid is a by-product of anaerobic metabolism which is subsequently metabolised in the liver[114]. It is produced when pyruvate (an intermediate metabolite from glycolysis) is metabolised under anaerobic conditions for Adenosine Triphosphate (ATP) generation and increased production occurs

when there is inadequate oxygen delivery. Intra-operative causes for this include: decreased cardiac output (e.g. general anaesthesia, reduced venous return, hypovolaemia), anaemia (blood loss), disturbances in gas exchange (ventilation/perfusion mismatch) and localised ischaemia (organ manipulation, vessel clamping, hypotension)[115]. Increased lactate may also be a result of reduced liver metabolism, which accounts for 40-50% of whole body lactate clearance[115] and may be affected by liver ischaemia, the Pringle manoeuvre (clamping of the hepatoduodenal ligament interrupting the flow of blood through the hepatic artery and portal vein)[116] and potentially from reduced metabolic capacity due to extensive resections. However no change in glucose and lactate metabolism following partial hepatectomy has been demonstrated in post-operative tests in either rats[117] or humans[114], implying that the liver has a large functional reserve under physiological conditions of lactate production. Finally, exogenous sources of lactate can raise the lactate level e.g. lactate containing fluids like Hartmann's solution and packed red cells.

Hyperlactataemia is associated with increased morbidity and mortality in a critical care setting[118], in patients with liver failure[119] and sepsis[120] and in those undergoing abdominal surgery[121] but it's association with outcome following liver surgery is less well described.

1.1.14 Pathological features of colorectal liver metastases

Liver specimens are routinely sent for pathological analysis after resection and the UK Royal College of Pathologists (RCPath) minimum dataset for liver specimens with colorectal metastases includes details of tumour number, size, location, resection margin clearance, capsular invasion, degree of

differentiation, the presence of tumour necrosis, vascular and lymphatic invasion, the presence of satellite lesions, invasion of adherent tissue, and lymph node status if sampled[122]. Other features whose prognostic significance has not been thoroughly assessed, include the presence of a fibrous pseudocapsule around the tumour and the degree of tumour necrosis. The presence of a pseudocapsule has been associated with better overall survival after resection of CRLM[123–125]. This issue is discussed in more detail in Chapter 9. Tumour necrosis can result from chemotherapy use[126] and is also seen in tumours with high rates of cellular turnover in rapidly expanding tumours[127]. Therefore, tumour necrosis may be associated with more aggressive tumours and a worse prognosis.

1.1.15 Socioeconomic status and outcomes in surgery

Lower socioeconomic status is associated with an increased risk of all-cause mortality and disease[128,129] It is also associated with poorer outcome from the treatment of disease. This may be due to many factors including unhealthy behaviour, environmental exposures or psychosocial factors[128]. There is also disparity in access to healthcare between populations of higher and lower socioeconomic status in the UK[130,131].

The incidence of primary colorectal cancer is associated with low socioeconomic status (SES) in the UK, where the age standardised incidence is 11% higher in men living in the most deprived areas of England compared with those living in the least deprived[132]. Population studies have also shown that low SES is associated with worse outcome amongst patients with colorectal cancer[133–135]. Little is known about the association between socioeconomic

status and outcome following liver resection for colorectal metastases and this is discussed further in Chapter 10.

1.1.16 Complications of liver surgery

Despite advances in both operative technique and perioperative care hepatic resection is associated with significant postoperative complications and mortality. Postoperative morbidity rates of between 12.5% and 66% (median 36%)[136,137] have been reported which include liver[137–139] and renal failure[140,141] and bile leak[142]. Similarly, mortality rates of between zero and 22% (median 3.7%)[136] are reported. Attempts have been made both to identify prognostic factors and develop prognostic scoring systems for both perioperative complications and death. Preoperative patient factors associated with adverse outcome are shown in Table 1.1.

Preoperative factor	Study reference
Hospital volume	143,144
Tumour type	143,145
Age	145–148
Gender	143,148–151
Hyperbilirubinaemia	148,151–157
Hypoalbuminaemia	63,148,157–161
Thrombocytopaenia	60,63,148,162
Renal dysfunction	63,148,153,163,164
Comorbidity	143,147,148,155,165,166
Diabetes mellitus	60,163,164
Chronic liver disease	145,146,167
Neutrophil:lymphocyte ratio	168

Table 1.1 Preoperative patient factors associated with adverse outcome following liver resection

Operative factors associated with adverse outcome are displayed in Table 1.2.

Operative factor	Study reference
Blood loss	60,61,164,169–171,148,152,153,155,156,159,162,163
Requirement for blood transfusion	60,62,172,63,146,149,154,157,162,165,167
Extent of resection	62,63,167,169,173–175,143,145,147–149,151,156,158
Duration of surgery	152,155,156,163,176–178
Extrahepatic procedures	63,172,179,180
Use of Pringle manoeuvre	149,165,167

Table 1.2 Operative factors associated with adverse outcome following liver resection

1.1.16.1 Post hepatectomy liver failure

Post-operative liver dysfunction is a major contributor to both morbidity and mortality with an incidence between 1.2% and 32% in published series[137–139,172,181–185]. It has been defined by the “50-50 criteria” as a prothrombin index of less than 50% (mean normal prothrombin time (PT) divided by patient's observed PT) and a serum bilirubin of >50µmol/L on the fifth postoperative day, which has been shown to predict liver failure and death after hepatectomy[186]. More recently post-hepatectomy liver failure (PHLF) and has been defined by the International Study Group of Liver Surgery (ISGLS) as a postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinaemia on or after postoperative day five[187].

1.1.16.2 Postoperative renal dysfunction

Newly developed postoperative renal dysfunction has also been shown to be associated with increased mortality following liver resection[188], with a reported incidence between 5-15%[140,141,189]. Post-hepatectomy renal failure may occur in conjunction with liver failure when maldistributive circulatory changes occur causing intravascular hypovolaemia[140,190], but is also related to operative stress and blood loss[148,152].

1.1.16.3 Bile leak

Bile leak following liver resection is a major cause of postoperative morbidity leading to longer hospital stay, the need for diagnostic tests and radiological or surgical intervention[191]. The incidence of bile leakage after liver resection without biliary reconstruction ranges from 3.6% to 12%[192,193] and after hepaticojejunostomy ranges from 0.4% to 31.8%[193,194]. Bile leak has been defined as discharge of fluid with an increased bilirubin concentration via the intra-abdominal drains on or after postoperative day 3 or as the need for radiological drainage or laparotomy for biliary complications. Increased bilirubin concentration in the intra-abdominal drain or within biliary collections are defined as a bilirubin concentration at least 3 times the serum bilirubin concentration measured at the same time. This may originate from the cut surface of the liver, from injury of the bile ducts, or from anastomotic leakage after bilioenteric anastomosis[195].

1.2 Problems to be investigated

1.2.1 How accurate is the regional Multidisciplinary Team (MDT) in determining tumour type and resectability?

Despite MDT assessment we have experienced cases where the histological diagnosis has either differed from the presumed preoperative diagnosis or where the available imaging does not allow a certain diagnosis to be made. Furthermore, despite advanced imaging techniques some patients undergo surgery without proceeding to resection due to unexpected operative findings. The aim of this study was to assess the performance of the MDT in its ability to determine accurately tumour type as well as resectability

1.2.2 What is the value of Magnetic Resonance Imaging (MRI) in addition to CT in the preoperative staging of colorectal liver metastases?

The aim was to measure the accuracy of CT and MRI in the detection of CRLM and to compare disease-free survival amongst those patients staged with CT alone and those staged with additional MRI.

1.2.3 Is there an association between the tumour doubling time of CRLM prior to liver resection and postoperative tumour recurrence and survival?

The aim of this study was to assess the DT of CRLM in patients not receiving liver-directed chemotherapy between radiological diagnosis and liver resection and to explore potential associations with tumour recurrence and survival after resection.

1.2.4 What happens to the size of CRLM in the interval between finishing liver-directed chemotherapy and liver resection and is this associated with tumour recurrence and survival?

Patients are allowed a period of recovery between completion of pre-operative chemotherapy for CRLM and liver resection[196] due to the potential hepatotoxicity of such agents[197]. During this period there is the potential for uninhibited tumour progression which may be associated with an increased chance of post-operative recurrence.

The aim of this study was to assess the change in size of CRLM between post-chemotherapy imaging and liver resection and to measure potential associations of this change with tumour recurrence and survival.

1.2.5 What is the association between hepatic steatosis, diabetes and obesity in patients undergoing liver resection and are these risk factors for major post-operative complications?

The aim of this study was to assess the relationship between diabetes, obesity and hepatic steatosis and identify any associations between these risk factors and major complications following liver resection

1.2.6 Does postoperative arterial lactate concentration predict post-operative organ dysfunction and mortality following liver resection?

The aim of this study was to determine whether the first post-operative lactate concentration is associated with 90-day mortality, length of hospital stay and organ dysfunction. It also aimed to identify which pre-operative and intra-operative factors are associated with the postoperative lactate concentration.

1.2.7 Can the International Study Group for Liver Surgery (ISGLS) definition of PHLF and postoperative renal dysfunction predict mortality after liver resection?

This study aimed to test the ability of the new definition of PHLF to predict mortality following liver resection. It also aimed to assess the incidence of renal dysfunction in the presence of PHLF following liver resection and its association with mortality.

1.2.8 Is the presence of a tumour pseudocapsule or tumour necrosis associated with recurrence after liver resection for colorectal liver metastases?

The aim of this study was to analyse the relative significance of factors reported in the minimum histopathology dataset and the presence of tumour pseudocapsules and necrosis on tumour recurrence one year after resection of CRLM.

1.2.9 Is socio-economic deprivation associated with the likelihood of undergoing liver resection for hepatic colorectal metastases and is it associated with outcome following surgery?

The primary aim of this study was to compare levels of socioeconomic deprivation in patients undergoing liver resection for CRLM in a regional HPB unit with those of the local population. A secondary aim was to determine if SES is associated with disease-free and overall survival.

1.3 Data collection

Since the inception of Peninsula HPB unit a detailed database of all cases undergoing surgery liver including those resected and those not resected. This database records many aspects of each patient's journey from referral to follow-up imaging and death. The database records routine data of use in clinical practice but also has been designed to answer specific questions by recording

novel aspects of the patient journey. Preoperative and operative data is entered by the operating surgeon at the end of resection. Details of postoperative complications, length of hospital stay, blood results and details of surveillance imaging are also recorded. Confirmation was obtained from the regional health research authority that under the harmonized Guidance Approval for Research Ethics Committees (REC), REC review was not required because patient data were collected during their normal hospital care and was anonymised for research purposes. No patient consent was required for this study.

Detailed statistical methods are included in each individual chapter.

Chapter 2 : The preoperative assessment of hepatic tumours - evaluation of UK regional multidisciplinary team performance

Wiggans MG, Jackson S A, Fox BMT, Mitchell JD, Aroori S, Bowles MJ, Armstrong EM, Shirley JF, Stell DA. (2013) The Preoperative Assessment of Hepatic Tumours : Evaluation of UK Regional Multidisciplinary Team Performance. *HPB Surg* 2013:861681.

DOI: 10.1155/2013/861681

2.1 Abstract

Introduction

In the UK patients where liver resection is contemplated are discussed at hepatobiliary multi-disciplinary team (MDT) meetings. The aim was to assess MDT performance by identification of patients where radiological and pathological diagnoses differed.

Methods

A retrospective review of a prospectively maintained database of all cases undergoing liver resection from March 2006 to January 2012 was performed. The presumed diagnosis as a result of radiological investigation and MDT discussion is recorded at the time of surgery. Imaging was reviewed by specialist gastrointestinal radiologists and results agreed by consensus.

Results

Four hundred and thirty-eight patients were studied. There was a significant increase in the use of preoperative imaging modalities (p=<0.01) but no change in the rate of discrepant diagnosis over time. 42 individuals were identified whose final histological diagnosis was different to that following MDT discussion (9.6%). These included 30% of patients diagnosed pre-operatively with hepatocellular carcinoma and 25% with cholangiocarcinoma of a major duct.

Discussion

MDT assessment of patients pre-operatively is accurate in terms of diagnosis. The highest rate of discrepancies occurred in patients with focal lesions without chronic liver disease or primary cancer, where hepatocellular carcinoma was over-diagnosed and peripheral cholangiocarcinoma under-diagnosed, where particular care should be taken. Additional care should be taken in these groups and pre-operative multi-modality imaging considered.

2.2 Introduction

Cancer care in the UK has undergone a major change in recent years with the centralisation of care in a network of Cancer Centres[198]. This has led to the establishment of regional Hepato-Pancreatico-Biliary (HPB) Units where patients in whom liver resection is contemplated are discussed at a Multi-Disciplinary Team (MDT) meeting in the presence of radiologists, oncologists, surgeons and physicians. This is intended to provide greater clinical input into the diagnosis of the wide spectrum of disease processes for which liver resection is appropriate[199]. During the same period increasing awareness of the

complimentary role of different imaging modalities in diagnosing liver disease[200–202] has led to many patients having multiple investigations prior to surgery. Although the accuracy of single imaging modalities including Ultrasound[200,203,204], Computerised Tomography (CT)[97,98,200,204,205], Magnetic Resonance Imaging (MRI)[97,98,200,204,206] and Positron Emission Tomography (PET)[200,205] scans in assessing hepatic malignancies have been well reported, the performance of MDT review of multiple pre-operative imaging techniques with input from clinicians in the diagnosis of malignancy and planning of treatment has not been described. The Peninsula HPB unit was founded in July 2005 to serve the Devon and Cornwall region of England (population 1.9 million). Imaging from referring hospitals is imported and discussed in a weekly MDT meeting and treatment recommendations made and recorded. After resection histology of the excised sample is also discussed at the MDT meeting. Despite MDT assessment we have experienced cases where the histological diagnosis has either differed from the presumed preoperative diagnosis or where the available imaging does not allow a certain diagnosis to be made. In this situation, a list of differential diagnoses is made from which treatment is recommended. Furthermore, despite advanced imaging techniques some patients undergo surgery without proceeding to resection due to unexpected operative findings. The primary aim of this study was to identify patients where the diagnosis determined by the MDT differed from the final histological diagnosis. A secondary aim was to identify recurring areas of confusion to guide future MDT assessment and to determine if the rate of inaccurate diagnosis of liver tumours and assessments of resectability of liver lesions has changed over time.

2.3 Methods

The Peninsula HPB unit has maintained a prospective database since the inception of the unit where the outcome of MDT discussion is recorded prior to surgery. A review of all patients undergoing surgery from March 2006 to January 2012 was performed. Details of pre-operative diagnosis, imaging modalities performed, operative findings and final histology were retrieved. Patients were identified where the MDT was unable to make a definitive diagnosis leading to differential options. All imaging was re-reviewed by a specialist gastrointestinal radiologist and results agreed by consensus. For comparison of utilisation of imaging modalities, the group was split in to two halves consisting of 219 patients each. The dataset was also divided to compare the earlier with later experience. Statistical analysis was performed using a chi square test or Mann-Whitney U test and a P-value of <0.05 was considered statistically significant. Analyses were performed using SPSS® version 20 (IBM, New York, USA).

2.4 Results

Four hundred and thirty-eight patients were identified including 248 males and 190 females with median age 65 years (range 21-90). The indications for surgery are shown in Table 2.1. Four hundred and seventeen patients underwent liver resection (95%) and 21 patients (5%) underwent surgery without resection. Details of the group not proceeding to resection are shown in Table 2.2.

2.4.1 Patient population

Primary MDT diagnosis	Number (%)	Median Age (Range)	Male/Female	Discrepant diagnosis (%)
Colorectal Liver Metastases (CRLM)	279 (64)	67 (33-90)	176/103	10 (3.6)
Hepatocellular carcinoma	44 (10)	63 (33-84)	31/13	13 (30)
Hilar Cholangiocarcinoma	28 (7)	67 (32-77)	14/14	7 (25)
Other metastases	24 (5)	62 (32-76)	8/16	1 (4)
Gall Bladder carcinoma	20 (5)	61 (41-82)	5/15	1 (5)
Neuroendocrine tumour (NET)	11 (3)	51 (41-77)	8/3	0 -
Metastasis of unknown origin	6 (1)	63 (43-73)	4/2	5 (83)
Biliary cystadenoma	6 (1)	34 (21-43)	0/6	0 -
Focal Nodular Hyperplasia (FNH)	5 (1)	34 (30-38)	0/5	0 -
Hepatocellular Adenoma	4 (<1)	31 (30-39)	0/4	0 -
Benign cyst	3 (<1)	52 (47-65)	0/3	1 (33)
Breast metastases	3 (<1)	67 (45-78)	0/3	3 (100)
Peripheral Cholangiocarcinoma	3 (<1)	70 -	2/1	1 (33)
Primary Sarcoma	1 (<1)	71 -	0/1	0 -
Haemangioma	1 (<1)	33 -	0/1	0 -
Total	438	65 (21-90)	248/190	42 (9.6)

Table 2.1 MDT indications for resection and number with discrepant histological diagnoses in 438 patients undergoing liver resection between March 2006 and January 2012

Final Diagnosis	Total	Number not resected (%)	Operative findings		
			Peritoneal disease	Disease progression	No/benign disease
Colorectal Metastases (CRLM)	270	7 (2.6)	4	3	0
Hepatocellular carcinoma	33	2 (6)	0	2	0
Hilar Cholangiocarcinoma	23	4 (17)	0	4	0
Gall Bladder Carcinoma (GBC)	19	2 (11)	2	0	0
Other metastases	30	3 (10)	1	2	0
Neuroendocrine Tumour (NET)	13	1 (8)	0	1	0
Haemangioma	9	1 (11)	0	0	1
Normal Liver	-	1	0	0	1
Total		**21 (4.8)**	**7**	**12**	**2**

Table 2.2 Reasons for non-resection in 21 patients undergoing surgery for planned liver resection between March 2006 and January 2012

2.4.2 Imaging performed

In total 969 imaging investigations (excluding repeat investigations of the same modality) were performed for the 438 patients including CT (432), MRI (227), PET (200), US (93), Octreotide scan (7) and ERCP (10). Only five patients did not have a CT scan. The number of MRI scans undertaken increased from 96 in the first half of the study (219 patients) to 131 in the second (P=0.001). Similarly, the number of PET scans undertaken increased from 85 to 115 (P=0.005).

The total number of investigations performed increased significantly during the study period from 442 in the first cohort to 525 in the second. Similarly, the median number of scans performed per patient increased from two (1-4) to three (1-4) (P<0.001).

2.4.3 Correlation of MDT assessment with operative findings

A decision not to resect at the time of surgery was made in 21 patients (4.8%) either because of peritoneal disease, tumour progression or because no malignant lesion could be identified (Table 2.2).

There was no change in the rate of non-resection over time (10/219 vs. 11/219). MDT assessment of operability was most accurate for CRLM where only 7/270 patients (2.6%) were not resected and least accurate for patients with hilar cholangiocarcinomas where 4/23 patients were not resected (P<0.001)

2.4.4 Correlation of MDT diagnosis with final pathology

Of the 438 patients operated on in this period 42 individuals were identified whose final histological diagnosis was different to the outcome of the MDT discussion (9.6%) (Table 2.3).

Histological diagnosis / MDT diagnosis	Total Discrepant	Angiomyolipoma* (1)	Benign cyst* (4)	Benign fibrosis* (3)	Bile duct papilloma* (1)	Breast metastasis (3)	Peripheral cholangiocarcinoma (11)	CRLM (270)	FNH* (6)	Focal fat* (2)	Haemangioma* (9)	Hepatocellular carcinoma (34)	NET (13)	No lesion* (2)	Sarcoma (4)	Chronic inflammation* (1)	Ovarian metastasis (5)	Xanthogranulomatous cholecystitis* (1)
Hepatocellular carcinoma (44)	**13**	1	-	-	-	-	5	1	-	1	2	-	2	-	-	1	-	-
Colorectal Metastases (CRLM) (279)	**10**	-	-	-	-	2	1	-	-	-	4	1	-	2	-	-	-	-
Hilar cholangiocarcinoma (31)	**7**	-	2	3	1	1	-	-	-	-	-	-	-	-	-	-	-	-
Metastases of unknown origin (6)	**5**	-	-	-	-	-	3	-	-	-	1	-	-	-	1	-	-	-
Breast metastases (3)	**3**	-	-	-	-	-	-	-	-	1	1	1	-	-	-	-	-	-
Peripheral cholangiocarcinoma (3)	**1**	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-
Anal metastases (7)	**1**	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-
Benign cyst (3)	**1**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-
Gall Bladder Carcinoma (20)	**1**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Total	**42**	**1**	**2**	**3**	**1**	**3**	**9**	**1**	**1**	**2**	**8**	**3**	**2**	**2**	**1**	**1**	**1**	**1**

Table 2.3 Discrepant diagnoses in 42 of 438 patients undergoing liver resection between March 2006 and January 2012

Total number of each diagnosis in the series (438) shown in brackets. All MDT diagnoses of Neuroendocrine Tumours (NET) (11), Focal Nodular Hyperplasia (FNH) (5), biliary cystadenoma (6), primary sarcoma (1) and haemangioma (1) were confirmed on histology. * Benign pathology

There was no change in the rate of discrepant diagnosis between the two study periods (23/219 vs. 19/219) (P=0.629). The median number of lesions per patient was one in both the first (range 0-9) and second (range 0-20) half of the series (P=0.057). Similarly, there was no difference in maximum tumour size with a median of 35mm (range 6-210) in the first half and 35mm (range 3-230) in the second (P=0.936). The median number of imaging modalities used was three in patients with discrepant diagnoses compared to two in those with correct diagnoses (P=0.003). The only difference occurred in the use of MRI where 31/42 (73.8%) patients with discrepant diagnoses had additional MRI compared to 196/396 (49.5%) patients where the diagnosis was correct (P=0.003). In total twenty-two patients (5%) underwent hepatic resection for what proved to be benign disease having been diagnosed with malignancy preoperatively. The difficult areas of MDT assessment fell into the following categories.

2.4.5 Hepatocellular cancer

Thirteen of 44 patients diagnosed as having hepatocellular carcinoma at MDT and proceeding to resection had different histological diagnoses after surgery, of which three were benign. There was no significant difference in the rate of discrepant diagnosis in those with and without a history of chronic liver disease (CLD) (6/19 vs. 7/25) (Table 2.4). In six patients with CLD the final histology revealed a mixed type of tumour with features of both hepatocellular carcinoma and cholangiocarcinoma. For the purposes of this study these have been classed as correct diagnoses.

Histology / MDT Diagnosis	Hepato-cellular carcinoma	Peripheral cholangio-carcinoma	Haem-angioma	Neuro-endocrine Tumour	Metastasis of Unknown Origin (MUO)	Hepatic sarcoma	Focal Nodular Hyperplasia	Angio-myolipoma	Total
Hepato-cellular carcinoma	18	4	1	1	-	-	-	1	25
Metastases of unknown origin	-	3	1	-	1	1	-	-	6
Peripheral cholangio-carcinoma	-	2	-	-	-	-	1	-	3
Total	18	9	2	1	1	1	1	1	34

Table 2.4 MDT and final histological diagnoses of 34 patients with peripheral liver lesions and no history of CLD or malignancy

2.4.6 Cholangiocarcinoma of major hepatic duct

All patients with suspected cholangiocarcinoma of a major hepatic duct underwent cholangiography (percutaneous, endoscopic or MR) in addition to cross sectional imaging. Seven of 28 patients diagnosed with cholangiocarcinoma at MDT had a different histological diagnosis after resection (Table 2.3). There was no significant difference in the rate of incorrect diagnosis in those who presented with obstructive jaundice (3/19) and those without (4/9). Of those patients diagnosed with cholangiocarcinoma without obstructive jaundice the diagnosis was confirmed in five patients on final histology.

2.4.7 Colorectal metastases

All patients diagnosed with CRLM had a history of colorectal cancer, but 10 (3.6%) had different histological diagnoses after resection (Table 2.3), of which six were benign. Six of these were metachronous lesions and four were synchronous with their colorectal cancer diagnosis (P=0.539).

2.4.8 Solid liver lesions with no history of chronic liver disease or primary malignancy

Thirty-four patients underwent resection of peripheral liver lesions (including hepatomas) with no history of CLD or primary malignancy of whom 13 had discrepant diagnoses (Table 2.4).

Peripheral cholangiocarcinoma was rarely diagnosed correctly pre-operatively. Of eleven patients with a diagnosis of peripheral cholangiocarcinoma at histology, only two had been diagnosed correctly preoperatively, both by

percutaneous biopsy. The remainder were inaccurately diagnosed as hepatocellular carcinomas or metastases (Table 2.3).

2.4.9 Adenoma/FNH/hepatocellular carcinoma

A group of 10, predominantly young, female patients (median age 33, range 33-63) was identified in whom the MDT differential list included FNH, adenoma or hepatocellular carcinoma. After resection, all patients had a histological diagnosis that was included in the alternatives made at MDT. In five patients, histology revealed hepatic adenoma, four revealed FNH and one a hepatocellular carcinoma.

2.5 Discussion

This study reveals a number of important features of the MDT assessment of patients with focal liver lesions during the six-year development of a regional HPB unit. Firstly, there has been a 50% increase in the number of imaging modalities used in the assessment of these patients over a short time interval. This has been caused by an increased utilisation of PET scans and MRI due to an increased awareness of their role and improved access. Although PET scans have poor sensitivity for detecting multiple liver lesions they are valuable in the pre-operative assessment of patients with CRLM to exclude extra-hepatic disease[207,208]. MRI scans with diffusion-weighted imaging have been shown to have greater sensitivity than CT in the detection of CRLM[205,209], hepatoma[210] and metastatic NET[211], although these scans have only been available to this

department since 2011. The policy of the unit is not to biopsy potentially resectable liver lesions due to the potential risk of tumour seeding[212,213].

In this series 21 patients (5%) did not undergo surgical resection, and the rate of non-resection did not change significantly over time. The rate of non-resection of liver lesions following assessment has been described previously with a reported rates of 3-12%[214,215]. The commonest cause of non-resection in our series was disease progression. The time interval between imaging and surgery may have a major impact on this outcome, limiting the value of modern imaging. Peritoneal disease was noted in seven of the unresected patients, which is not readily identified by any imaging modality[216].

The highest rate of discrepancies in our series occurred in the group of patients with focal liver lesions without a history of chronic liver disease or primary cancer. This finding emphasises the importance of assessing imaging in the context of the clinical history (13/34). Two observations arise from this group of significance in clinical practice. Firstly, the majority of patients (5/6) diagnosed with metastases of unknown origin (MUO) have defined histology after resection, of which the most common is peripheral cholangiocarcinoma. These lesions typically have hypovascular appearances on imaging with ring-like enhancement[217] and can easily be misdiagnosed as colorectal or breast metastases[218]. Published guidelines for the management of MUO recommend a range of chemotherapy regimens[51], none of which have been shown to be of benefit in the treatment of cholangiocarcinoma, whereas surgical resection of peripheral cholangiocarcinoma is of proven benefit[219], but is rarely appropriate in the treatment of MUO. Similarly, 4/25 patients diagnosed as having hepatocellular carcinoma in this setting are ultimately shown to have peripheral

cholangiocarcinoma. Peripheral cholangiocarcinoma is less common than hepatocellular carcinoma[220] which may lead to a low index of suspicion in MDT diagnosis.

In patients with a history of CLD and focal liver lesions there remains a high rate of patients found not to have hepatocellular carcinoma after excision (7/19). These include neuroendocrine metastases which are hypervascular lesions having similar radiological appearances to hepatoma. This has implications for this patient group where treatment is often recommended without a histological diagnosis.

The commonest indication for liver resection in our series has been CRLM and the rate of discrepant diagnoses for this group is low (3.6%). The most common alternative diagnosis after resection in this group was haemangioma. The radiological characteristics of this group have been described elsewhere[221] and can be difficult to distinguish from metastases. Interestingly two patients in this group were found to have breast cancer metastases after primary breast surgery two and ten years previously. Breast metastases can have similar radiological features to CRLM and can occur many years after the primary diagnosis. A further breast metastasis occurred as an obstructing lesion of the left hepatic duct sixteen years after primary surgery and was diagnosed as a hilar cholangiocarcinoma.

The high rate of discrepant diagnoses in patients with major duct cholangiocarcinoma has been shown previously[222–224]. These lesions are usually sclerosing adenocarcinomas causing biliary obstruction and are often not visible as a mass lesion[217]. In this situation, the presence of the lesion is

inferred by the radiological finding of ductal dilation along with clinical features of obstruction. The most common alternative diagnosis in this series was ductal fibrosis. This condition may be a manifestation of an autoimmune process and can have similar radiological features to cholangiocarcinoma[225]. Peribiliary cysts can often be diagnosed preoperatively by the presence of multiple cysts, but can also mimic cholangiocarcinoma[217] as in the two cases experienced in this series. The most difficult lesions to both assess and make treatment recommendations for are peripheral ductal lesions which do not cause jaundice but are found coincidentally or cause cholestasis. In these patients, often the only finding is a short segment of dilated intrahepatic duct. In this series 5/9 of these patients were found to have a cholangiocarcinoma on final histology and surgery for these lesions is therefore justified, particularly as these lesions can usually be resected safely without the need for resection of the extra-hepatic biliary tree.

A particularly difficult group of patients to assess and make treatment recommendations for is the group of predominantly young women with primary liver lesions where the differential diagnosis includes hepatocellular carcinoma, adenoma and focal nodular hyperplasia. These lesions are usually single but may be multi-focal and often occur on a background of obesity or oral contraceptive use[226]. In this series 6/10 lesions were shown to be neoplastic on final histology (adenoma or hepatocellular carcinoma) and surgery appears justified in this patient group.

Overall 5% of patients underwent surgery for misdiagnosed benign lesions, which is similar to earlier experience[227]. The most common benign lesions were haemangiomas which can be hypo-, iso- or hyper-attenuating on imaging and

can sometimes increase in size[221], making distinction from malignant tumours difficult.

In conclusion, approximately 10% of patients proceeding to surgery following discussion at the HPB MDT are subsequently shown to have an inaccurate diagnosis and 5% are understaged. Despite an increase in the number of imaging modalities used there has been no change in this rate over time.

These discrepancies must be considered by clinicians in the context of the risk of over-staging resectable disease or misdiagnosing malignant lesions as benign. The implications of this should be discussed with patients prior to embarking on liver resection to better enable them to make informed decisions about their management. Furthermore, MDTs should keep record of cases with discrepant diagnoses for discussion to learn from them and aid future diagnostic challenges.

Chapter 3 : Assessment of the value of MRI scan in addition to CT in the pre-operative staging of colorectal liver metastases

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3.1 Abstract

Introduction

The aim of this study was to measure the accuracy of CT and MRI scans in detecting colorectal liver metastases (CRLM) and to determine if patients who are staged with MRI in addition to CT have a longer liver recurrence-free survival compared to those having CT alone in a unit performing routine intra-operative ultrasound.

Methods

A retrospective analysis of patients undergoing liver resection for CRLM was performed. Patients staged preoperatively with CT or with additional MRI were included and those with additional PET imaging were excluded from survival analysis. Timing and site of tumour recurrence were recorded.

Results

During a seven-year period 303 patients underwent resection for CRLM of whom 47 (15.5%) were staged with CT alone, 36 (11.9%) with additional MRI.

The overall accuracy of CT (63%) and MRI (61.9%) was similar in the detection of tumour nodules (P=0.905). There was no difference in the rate of intra-hepatic recurrence between groups with 13/47 and 8/36 cases respectively (P=0.737). There was no difference in the disease-free survival curves between the groups (P=0.487).

Discussion

Our recommendation is that MRI should not be a mandatory imaging modality in referral guidelines for patients with hepatic CRLM, as the cost and delay associated with the scan outweigh any potential benefit in terms of improved sensitivity compared to CT.

3.2 Introduction

Pre-operative imaging is undertaken in the preparation of patients for resection of hepatic colorectal metastases (CRLM) to exclude extra-hepatic disease and to define the site, size and number of hepatic lesions. Most patients have computerised tomography (CT) scans undertaken as an initial investigation, which has a been shown in a meta-analysis to have a sensitivity of 63.8% (95% CI 54.4-72.2) for the detection of metastatic lesions[205]. Magnetic Resonance Imaging (MRI) scans with hepatobiliary contrast media have been shown to have greater sensitivity for the detection of sub-centimetre lesions[97] and have therefore been recommended in the pre-operative staging of such patients in the most recent guidelines adopted by International Hepatopancreatobiliary Association (IHPBA)[95]. Use of this imaging modality allows detection and treatment of smaller lesions within the liver which would potentially be

overlooked by CT. Additional use of MRI potentially therefore may lead to a lower rate of intrahepatic recurrence after resection compared to patients staged with CT alone. This hypothesis has not however been formally tested. In addition, many surgeons use intra-operative ultrasound (IOUS) to define hepatic lesions prior to resection. Although IOUS is operator-dependent, it has high sensitivity in the detection of sub-centimetre hepatic lesions and has been shown to influence operative planning[228]. Therefore, the use of IOUS may remove any added benefit of performing MRI scans in addition to CT scans during preoperative staging.

The aim of this study was to measure the accuracy of CT and MRI scans in detecting hepatic metastases and to determine if patients who are staged with MRI in addition to CT have a longer liver recurrence-free survival compared to those having CT alone in a unit performing routine IOUS.

3.3 Methods

A retrospective analysis of data retrieved from a prospectively maintained database of all patients undergoing liver resection for CRLM between July 2005 and September 2012 was performed. Patients are referred from five hospitals within the South West Peninsula and all imaging is performed at the local hospital. Peninsula Hepatopancreatobiliary (HPB) unit referral guidelines for CRLM do not mandate the use of pre-operative MRI or PET scans, although these are often undertaken at the discretion of referring clinicians, according to personal preference. As CT and MRI scans were performed over a seven-year period at five hospitals a number of different liver protocols were used. Pre-

operative imaging of all patients was reviewed at the regional HPB meeting by specialist HPB radiologists and outcomes recorded in the database, including tumour size and number. For patients undergoing liver surgery IOUS was performed using a Toshiba Nemio®. Liver resection was undertaken using standard techniques, to remove all abnormalities observed with IOUS. The exact number of lesions observed with IOUS was not however recorded. The size and number of lesions found on pathological examination of the resection specimen was recorded. The number of lesions detected on pre-operative imaging with CT and MRI scans was compared to the number found on histological examination in patients undergoing resection. Patients were considered to be accurately staged when an identical number of lesions were found at histology as was seen at imaging, understaged when more lesions were found on histology and overstaged when lesions were identified on imaging which were not confirmed to be CRLM by histological examination. Routine data relating to primary tumour pathology, the use of adjuvant chemotherapy, and pre-operative blood tests were also recorded. Patients were followed-up postoperatively by clinical review and telephone contact. Post-operative surveillance CT scans were performed at six-monthly intervals for three years and annually to five years after resection. The timing and site of tumour recurrence were recorded as well as dates of death. Follow-up was completed at March 2013.

PET scans have a high sensitivity in the detection of hepatic metastases[205] and to avoid potential bias patients were excluded from survival analysis if they had a PET scan undertaken as part of pre-operative staging. Patients were also excluded if they died without undergoing surveillance imaging, or underwent

planned palliative resections. Patients who developed cut surface recurrences following a resection with a positive margin (R1) were also excluded as these were deemed to have been due to technical failure.

Survival curves were constructed using SPSS® by the Kaplan-Meier method and differences in survival were assessed using the log rank method. In analysis of intra-hepatic recurrence survival time was censored if patients developed extra-hepatic recurrence as no further surveillance imaging was recorded. Comparison between groups was performed using chi square or Mann Whitney U test as appropriate. Potential associations between pre- and intra-operative factors, as well as histological outcome and tumour recurrence were tested using univariate logistic regression or chi-square test at the level of $P< 0.25$[229], as appropriate. Significant variables in the univariate analysis were included in the multivariate logistic regression model and were considered to be significant if $P< 0.05$. Univariate and multivariate analyses were carried out using the statistical package R 2.1.14[230].

3.4 Results

Data relating to 303 patients were analysed. All patients underwent a pre-operative CT scan, 168 patients (55.4%) also had an MRI scan, 209 patients (69.0%) had a PET scan and 135 patients had a CT only (44.6%). In the subset of patients who had an MRI in addition to CT the median number of lesions identified on pre-operative imaging was greater than in those having CT alone (P<0.001) (Table 3.1).

N=303	Median number of lesions on imaging (Range)	Median number of lesions on pathology (Range)	Number accurate (%)	Number understaged (%)	Number overstaged (%)
CT only group (n=135)	1 (0-8)	1 (1-9)	85 (63.0)	37 (27.4)	13 (9.6)
Additional MRI group (n=168)	2 (0-11)	2 (0-10)	104 (61.9)	27 (16.1)	37 (22.0)
P-Value	<0.001*	0.063	0.905	0.001*	

Table 3.1 Accuracy of CT and MRI in 303 patients undergoing liver resection for CRLM staged preoperatively with either CT alone or with additional MRI.

***Significant at the level of 0.05**

However, there was no difference in the proportion of patients accurately staged in terms of tumour number by each modality. A similar proportion of patients were understaged by CT (27.4%) as were over staged by MRI (22.0%). During the study period, a decision not to resect was made at the time of surgery in five patients (1.6%) due to either the presence of peritoneal disease (n=4) or intrahepatic disease progression (n=1). Three of these patients were staged with CT alone, one had additional MRI, and one an additional PET scan.

In the survival analysis 209 patients who had a PET scan as part of tumour staging were excluded. An additional 11 patients were excluded either because they died before their first surveillance scan (n=4), had a non-curative resection (n=3), or had cut surface recurrence after an R1 liver resections (n=4), leaving 83 patients for analysis. Of these, 47 (56.7%) were staged with CT alone and 36 (43.4%) with additional MRI. The median interval from CT to surgery was 57 days (20-148) in patients staged with CT alone compared to 91.5 days (21-189) in those staged with additional MRI (P=0.037). Characteristics of the 83 patients used in survival analysis are shown in Table 3.2.

The median follow up time was 1.67 years for those staged with CT alone (range 0.19-7.19) and 1.67 for those with CT and MRI (range 0.37-6.71) (P=0.900). The median number of post-operative surveillance scans performed was three (range 1-9) in the CT alone group and 2.5 (range 1-9) in the group with CT and MRI (P=0.959).

N=83		CT only (n=47)		CT and MRI (n=36)		P-value
		Median (Range)	Count (%)	Median (Range)	Count (%)	
Age		69 (33-87)		68 (36-87)		0.840
Gender	Female		16 (34.0)		10 (27.8)	0.636
	Male		31 (66.0)		26 (72.2)	
T stage	1		1 (2.1)		0 (0.0)	0.614
	2		1 (2.1)		2 (5.6)	
	3		37 (78.7)		26 (72.2)	
	4		6 (12.8)		7 (19.4)	
	Unavailable		2 (4.3)		1 (2.8)	
N stage	0		21 (44.7)		18 (50.0)	0.915
	1		14 (29.8)		10 (27.8)	
	2		10 (21.3)		7 (19.4)	
	Unavailable		2 (4.3)		1 (2.8)	
Apical node	-ve		36 (76.6)		24 (66.7)	1.000
	+ve		5 (10.6)		3 (8.3)	
	Unavailable		6 (12.8)		9 (25.0)	
Site of primary tumour	Right		11 (23.4)		7 (19.4)	0.712
	Left		10 (21.3)		6 (16.7)	
	Rectum		26 (55.3)		23 (63.9)	
Timing	Synchronous		24 (51.1)		17 (47.2)	0.826
	Metachronous		23 (48.9)		19 (52.8)	
Preoperative chemotherapy	No		26 (55.3)		18 (50.0)	0.663
	Yes		21 (44.7)		18 (50.0)	
Neutrophil:lymphocyte ratio (pre-op)		2.9 (1.0-17.3)		2.5 (1.2-9.1)		0.591
Surgical approach	Open		44 (93.6)		35 (97.2)	0.629
	Laparoscopic		3 (6.4)		1 (2.8)	
RFA included	No		46 (97.9)		35 (97.2)	1.000
	Yes		1 (2.1)		1 (2.8)	
Wedge resection included	No		38 (80.9)		24 (66.7)	0.203
	Yes		9 (19.1)		12 (33.3)	
Extent of resection	Minor		19 (40.4)		11 (30.6)	0.490
	Major		28 (59.6)		25 (69.4)	
Repeat operation	No		44 (93.6)		36 (100.0)	0.254
	Yes		3 (6.4)		0 (0.0)	
Number of liver lesions		1 (0-7)		1 (1-7)		0.932
Diameter of largest tumour (mm)		37 (3-119)		30 (6-95)		0.085
Resection margin <1mm	No		43 (91.4)		31(86.1)	0.496
	Yes		4 (8.6)		5 (13.9)	
Hepatic steatosis	<33%		38 (80.9)		29 (80.6)	1.000
	33-66%		8 (17.0)		6 (16.7)	
	>66%		1 (2.1)		0 (0.0)	
	Not reported		0 (0)		1 (2.8)	

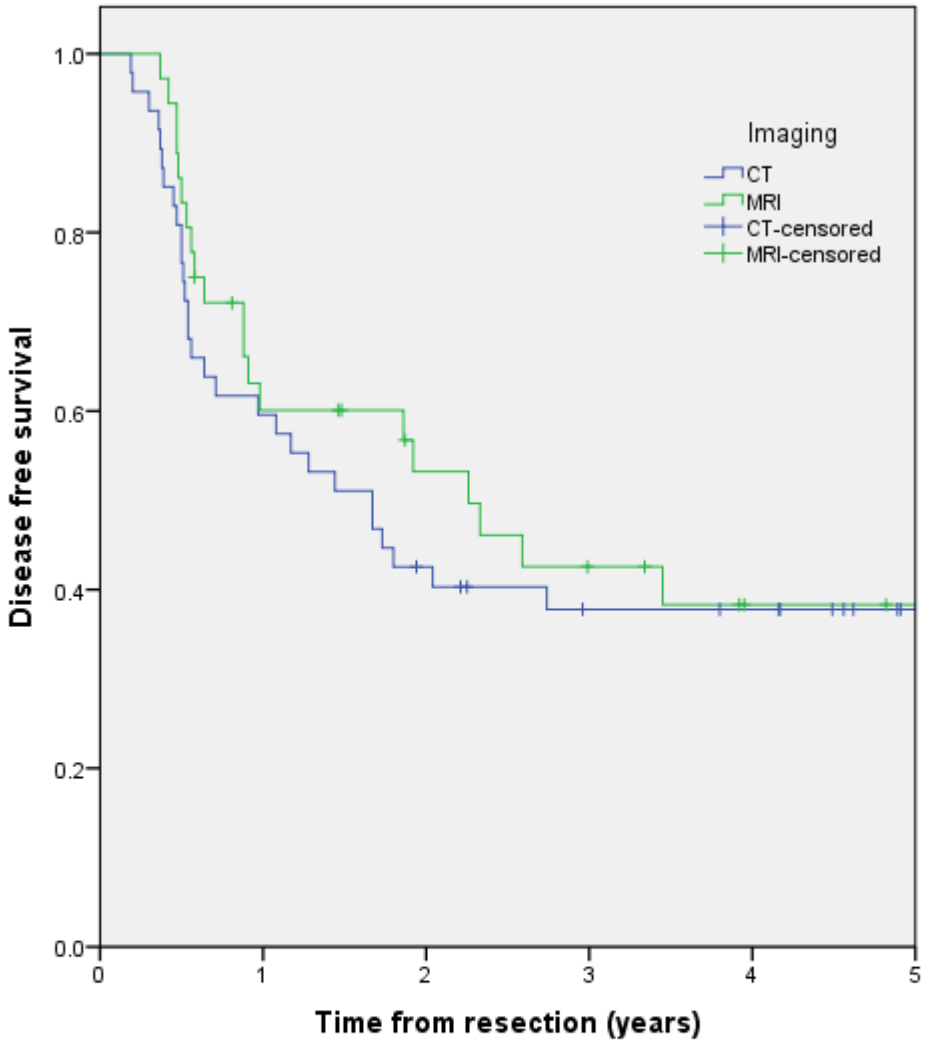
Table 3.2 Characteristics of 47 patients staged preoperatively with CT alone and 36 patients staged with additional MRI undergoing liver resection for CRLM

N=83		CT only (n=47)	CT and MRI (n=36)	P-value
		Count (%)	Count (%)	
Tumour Recurrence	Yes	29 (61.7)	20 (55.6)	0.573
	No	18 (38.3)	16 (44.4)	
Intrahepatic recurrence	Yes	13 (27.7)	8 (22.2)	0.573
	No	34 (72.3)	28 (77.8)	
Extrahepatic recurrence	Yes	20 (42.6)	15 (41.7)	1.000
	No	27 (57.4)	21 (58.3)	
Death	Yes	18 (38.3)	14 (38.9)	1.000
	No	29 (61.7)	22 (61.1)	

Table 3.3 Details of tumour recurrence and death in 47 patients staged preoperatively with CT alone and 36 patients staged with additional MRI undergoing liver resection for CRLM

Forty-nine patients (59.0%) suffered tumour recurrence during follow-up (Table 3.3) with a median time to recurrence of 7 months (range 71 days – 3.5 years).

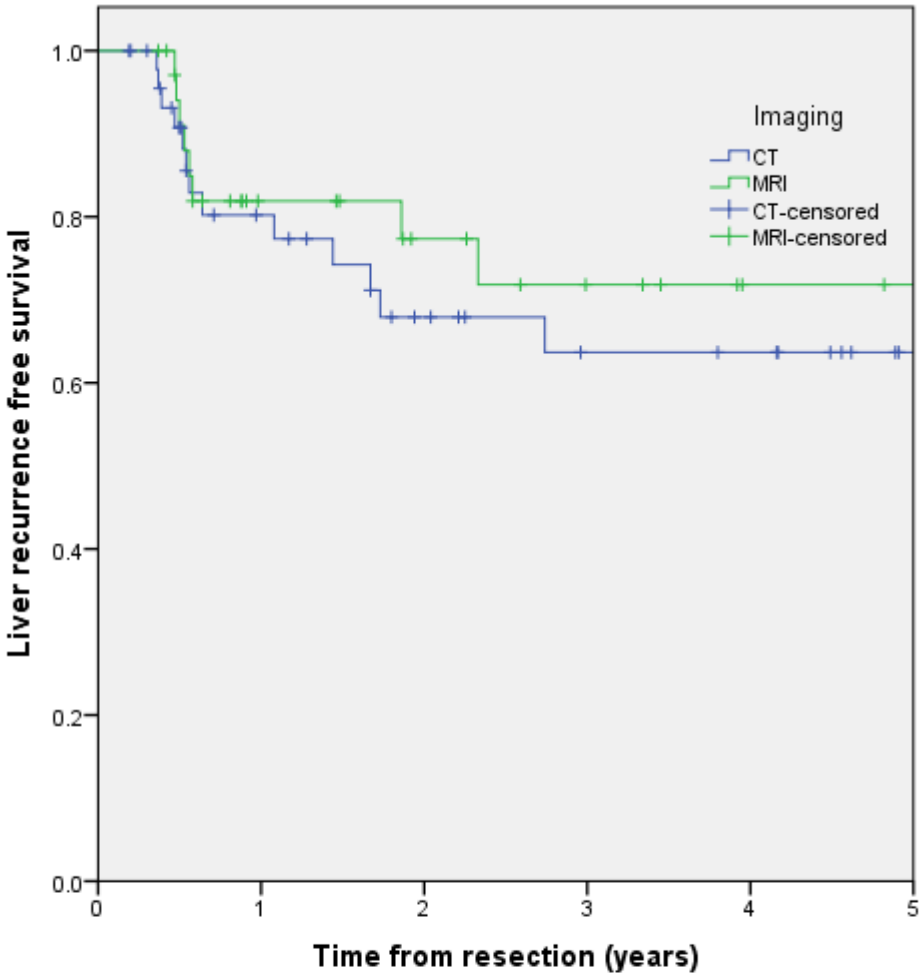
There was no significant difference in the overall recurrence rates of those staged preoperatively with CT alone (29/47) and those who had additional MRI (20/36) (P=0.573). The median time to recurrence was also similar between groups (0.54 vs 0.76 years) (P=0.682). Similarly, there was no significant difference in the disease-free survival between groups (P=0.548) (Figure 3.1).



CT						
Number at risk	47	28	19	14	13	6
Cumulative number of events		19	27	29	29	29
MRI						
Number at risk	36	20	15	11	7	6
Cumulative number of events		14	16	19	20	20

Figure 3.1 Kaplan–Meier disease free survival curves following liver resection for CRLM for 47 patients staged preoperatively with CT alone and 36 patients staged with additional MRI (Log rank P=0.366)

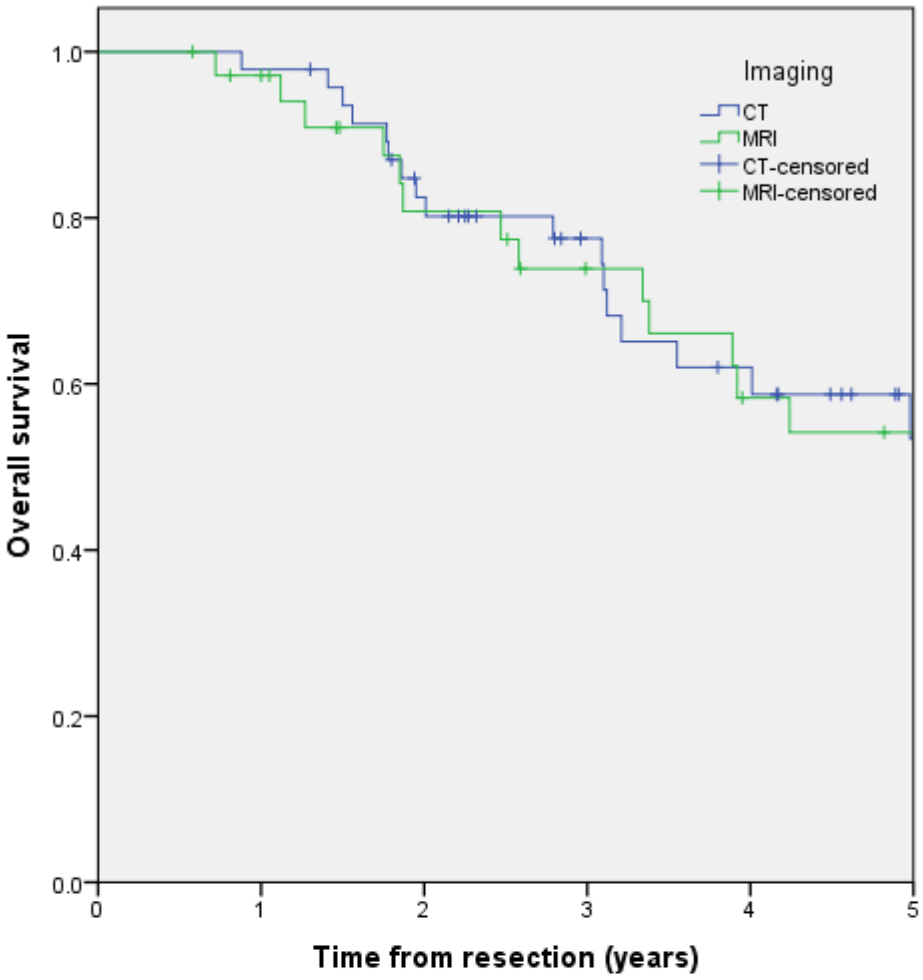
The majority of tumour recurrences in both those staged with CT alone (20/29) and those with additional MRI (15/20) were extra-hepatic (P=1.000). There was no significant difference in the rate of intra-hepatic recurrence between those staged with CT alone (13/47) and those staged with CT and MRI (8/36) (P=0.573). The liver recurrence-free survival curves for those staged with CT alone and those with additional MRI revealed a 5.5% difference at five years, which did not reach significance (P=0.491) (Figure 3.2). A sample size of 1942 patients would be needed to confirm the significance of this observed difference in liver recurrence-free survival.



CT						
Number at risk	47	28	19	14	13	6
Cumulative number of events		8	12	13	13	13
MRI						
Number at risk	36	20	15	11	7	6
Cumulative number of events		6	7	8	8	8

Figure 3.2 Kaplan–Meier liver survival curves of liver recurrence free survival following liver resection for CRLM for 47 patients staged preoperatively with CT alone and 36 patients staged with additional MRI (Log rank P=0.487) In cases where patients developed only extrahepatic recurrence, liver recurrence free survival was censored at the time of extrahepatic recurrence

There were 32 deaths during the study period with a similar proportion of deaths within each group (18/47 vs 14/36) (P=1.000). There was no difference in overall survival between patients staged preoperatively with CT alone or with additional MRI (Figure 3.3) with actuarial 5-year survival rates of 61% in both groups (P=0.962).



CT						
Number at risk	47	46	36	25	19	10
Cumulative number of events		1	8	10	15	17
MRI						
Number at risk	36	33	24	19	14	12
Cumulative number of events		1	6	8	12	13

Figure 3.3 Kaplan–Meier liver overall survival curves following liver resection for CRLM for 47 patients staged preoperatively with CT alone and 36 patients staged with additional MRI (Log rank P=0.969)

Multivariate analysis of factors associated with overall tumour recurrence (Table 3.4) demonstrated no association between the additional use of MRI during preoperative staging and tumour recurrence (P=0.573). Only the site of the primary colorectal cancer was associated with overall tumour recurrence with rectal cancer more than trebling the risk of recurrence compared to colonic cancer (P=0.036). Analysis of factors associated with intra-hepatic recurrence did not demonstrate any association with the pre-operative use of MRI (P=0.573) but revealed that the nodal stage of the primary tumour and inclusion of a wedge resection were associated with intra- hepatic recurrence (Table 3.4). Positive nodal stage increased the risk of recurrence by a factor of 3.9 (P=0.038) and the inclusion of a wedge resection had the greatest effect increasing the risk by a factor of six (P=0.002).

		Any recurrence			Intrahepatic recurrence		
N=83		**Univariate**	**Multivariate**		**Univariate**	**Multivariate**	
		P-Value	**P-Value**	**Coef (95% CI)**	**P-Value**	**P-Value**	**Coef (95% CI)**
Age		0.363			0.363		
Gender		0.866			0.094*	0.111	
T stage of primary	1 vs 2	0.147*	0.991		0.644		
	2 vs 3		0.995				
	3 vs 4		0.995				
N stage of primary	0 vs 1	0.828			0.119*	0.038**	3.86 (1.17-12.75)
	1 vs 2					0.837	
Apical node positive		0.890			0.598		
Site of primary colorectal tumour	Right vs Left	0.041*	0.147		0.610		
	Left vs Rectum		0.036**	3.67 (1.15-11.66)			
Timing	Synchronous vs Metachronous	0.723			0.283		
Preoperative chemotherapy		0.366			0.749		
Neutrophil:lymphocyte ratio (pre-op)		0.977			0.618		
Surgical approach	Open vs Laparoscopic	0.708			0.546		
Wedge resection included		0.071*	0.138		0.003*	0.002**	5.99 (1.92-18.67)
Extent of resection	Major vs minor	0.289			0.633		
Redo operation		0.378			0.726		
Number of liver lesions		0.977			0.029*	0.234	
Diameter of largest tumour (mm)		0.324			0.794		
Resection margin <1mm		0.369			0.805		
Hepatic steatosis	<33% vs >33%	0.206*	0.254		0.451		
MRI		0.573			0.573		

Table 3.4 Univariate and multivariate analysis of factors associated with tumour recurrence following liver resection for CRLM in 83 patients staged with either CT alone (n=47) or with additional MRI (n=36)

***Significant at the level of 0.25 for univariate analysis and included in multivariate analysis **Significant at the level of 0.05 for multivariate analysis**

3.5 Discussion

There are two main findings to the study. Firstly, CT and MRI have similar rates of accuracy in identifying the number of CRLM in patients undergoing hepatic resection while CT has a greater tendency to understage, and MRI to overstage patients in terms of tumour number. Secondly there is no benefit in terms of overall or intra-hepatic tumour recurrence rate, and overall or intra-hepatic recurrence-free survival following liver resection of patients undergoing staging with MRI scan in addition to CT, when IOUS is used.

Although guidelines for the preoperative assessment of patients with colorectal liver metastases state that all patients should undergo CT of the chest, abdomen and pelvis[122], the role of liver MRI in this context is less clearly defined. A consensus statement recommended that when expertise is available contrast-enhanced MRI is better for detecting and characterising liver lesions, particularly those that are sub-centimetre in diameter[95], as two meta-analyses demonstrated a clear benefit of MRI over CT in the detection of these lesions[231,232] a finding that has been demonstrated more recently in patients who have undergone neoadjuvant chemotherapy[233]. However, the disadvantages of the use of MRI were not considered in this recommendation. The average cost of an abdominal MRI scan in the USA is $2625[234] which must be considered when measuring its potential benefit. More importantly the current study revealed that the median time to resection was 35 days longer in patients who were staged with additional MRI. This delay is contributed to by resource issues in a publicly-funded healthcare system and the need for further MDT discussion, has the potential to allow tumour progression prior to surgery and probably contributes to patient anxiety.

This study used accuracy in patient staging rather than lesion-based sensitivity and specificity as a measure of test utility. The results demonstrate that fewer patients were understaged with MRI as fewer lesions were missed compared to CT but also revealed that MRI tended to overstage patients. The ability of MRI to identify lesions not seen on CT conferred no measurable benefit in our series as these small lesions are likely to be identified at the time of surgery either by palpation or the use of IOUS. In this context, the tendency of MRI to overstage hepatic CRLM may be more significant as patients may potentially be denied surgery if lesions are falsely identified.

This study is unusual in that in addition to an assessment of the accuracy of imaging compared with histology we have attempted to assess the clinical value of an imaging modality in terms of tumour recurrence and patient survival, and have shown no clinical benefit in the use of MRI. This is a more compelling assessment of the value of an imaging modality than a correlative study with pathology. It should be noted that 68% of patients undergoing resection were staged preoperatively with PET in addition to CT. PET has similar sensitivity and specificity to MRI in the detection of liver lesions[232]. To avoid bias these patients were excluded from survival analysis. One other study has attempted to assess the value of MRI in terms of patient outcome[235], and found a benefit in terms of hepatic recurrence. This study however did not exclude patients who had PET scans as part of pre-operative staging, undermining the strength the finding.

A weakness of the study is the lack of consistent details relating to MRI and CT scan protocols due to geographical variation and improving technology during the study period. The question of determining the additional value of MRI scans

in CRLM staging can only accurately be assessed by a randomised controlled trial. Such a study is unlikely ever to take place due to the huge number of patients required and the fact that improving technology would very rapidly render the results obsolete. The question can therefore best be addressed by retrospective assessment, in which context heterogeneity of the imaging protocols undertaken adds to the value of the study as the standards required in clinical trials may not be routinely reproduced in all hospitals.

It is likely that the decision to request an MRI scan in addition to CT is taken in potentially more difficult cases, for example where there has been difficulty in accurate characterisation of liver lesions or where a large number of small lesions is suspected. This is a potential source of bias in the interpretation of crude survival data. To allow for this problem a multivariate analysis was performed to include commonly identified risk factors for recurrence and survival after liver resection, along with the additional use of MRI in pre-operative staging. This analysis revealed that the additional use of MRI scans in pre-operative imaging has no association with tumour recurrence at any site, or with patient survival.

Our recommendation is that MRI should not be a mandatory imaging modality in referral guidelines for patients with hepatic CRLM, as the cost and delay associated with the scan outweigh the potential small benefit in terms of improved sensitivity compared to CT. This recommendation depends upon the use of IOUS, which can be performed with low cost and does not impose any delay in the patient pathway prior to surgery. Further studies should be carried out to assess the impact of the use of MRI on patient outcomes rather than the ability of MRI to detect individual lesions and these should consider how the

benefit of MRI may have improved with newer scanners, protocols and contrast agents.

Chapter 4 : The pre-operative rate of growth of colorectal metastases in patients selected for liver resection does not influence post-operative disease-free survival

Wiggans MG, Shahtahmassebi G, Aroori S, Bowles MJ, Briggs C, Stell DA. (2016) The pre-operative rate of growth of colorectal metastases in patients selected for liver resection does not influence post-operative disease-free survival. *Eur J Surg Oncol* 42:426–32.

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4.1 Abstract

Introduction

To assess the potential association between the change in diameter of colorectal liver metastases between pre-operative imaging and liver resection and disease-free survival in patients who do not receive pre-operative liver-directed chemotherapy.

Methods

Analysis of a prospectively maintained database of patients undergoing liver resection for colorectal liver metastases between 2005 and 2012 was undertaken. Change in tumour size was assessed by comparing the maximum tumour diameter at radiological diagnosis determined by imaging and the maximum tumour diameter measured at examination of the resected specimen in 157 patients.

Results

The median interval from first scan to surgery was 99 days and the median increase in tumour diameter in this interval was 38%, equivalent to a tumour doubling time (DT) of 47 days. Tumour DT prior to liver resection was longer in patients with T1 primary tumours (119 days) than T2-4 tumours (44 days) and shorter in patients undergoing repeat surgery for intra-hepatic recurrence (33 days) than before primary resection (49 days). The median disease-free survival of the whole cohort was 1.57 years (0.2-7.3) and multivariate analysis revealed no association between tumour DT prior to surgery and disease-free survival.

Discussion

The rate of growth of colorectal liver metastases prior to surgery should not be used as a prognostic factor when considering the role of resection.

4.2 Introduction

Although the survival of patients with untreated metastatic colorectal cancer has been described[108] the rate of growth of untreated colorectal liver metastases (CRLM) has not been defined, as patients will either receive active treatment or be treated with palliative intent where assessment of tumour progression is rarely undertaken. CRLM may sustain a period of growth between diagnosis and treatment, and assessment of change in tumour size in this period allows an estimate of growth rate. Liver resection provides a potential cure for patients

with CRLM with five-year survival rates ranging from 32-65%[40,41]. Factors shown to affect survival include CEA estimation[236], tumour number[236–238], tumour size[236,238,239], resection margin involvement[236,238,240], the presence of satellite lesions[241], the ratio of neutrophils to lymphocytes in peripheral white blood cells[168] and the response to liver-directed chemotherapy[242]. Little information however is available regarding the influence of the pre-operative rate of growth of CRLM, often expressed as tumour doubling-time (DT), on survival following liver resection.

The aim of this study was to assess the DT of CRLM in patients not receiving liver-directed chemotherapy between radiological diagnosis and liver resection and to explore potential associations with tumour recurrence and survival after resection.

4.3 Methods

Analysis of data retrieved from a prospectively maintained database of 319 patients undergoing liver resection for CRLM between May 2004 and December 2012 was performed. One hundred and fifty-five patients receiving liver-directed chemotherapy were excluded. Imaging was performed with either computerised tomography (CT) or magnetic resonance imaging (MRI) and reviewed at the specialist HPB MDT. The diameter of the largest lesion was measured and recorded in the database for research purposes. Change in tumour size was assessed by comparing the maximum tumour diameter at radiological diagnosis and the maximum tumour diameter measured at examination of the resected specimen. Change in size was expressed as a function of time. Tumour DT was calculated using the equation:

$$DT=Ti \times Log2 / (3 \times Log(Dp/Dr)$$

where Ti = time interval between radiological diagnosis and surgery, Dp = diameter at pathology and Dr = diameter at radiological diagnosis [107].

Data relating to primary and secondary tumour pathology and other routine clinical information were retrieved. Liver resections were defined according to the Brisbane classification [17] and undertaken using standard techniques. Major resections were defined as resections of four or more segments [243].

Synchronous metastases were defined as those diagnosed prior to or within two months of primary surgery. Post-operative follow-up included surveillance CT scans at six-monthly intervals for three years and annually to five years after resection. The timing and site of tumour recurrence were recorded as well as dates of death. Follow-up was completed at March 2014.

Patients were excluded from survival analysis if they died without undergoing surveillance imaging or underwent palliative resections. Patients who developed tumour recurrence at the resection surface following a resection with a positive margin (R1) were excluded as these were deemed to have been due to technical failure rather than tumour recurrence.

Survival curves were constructed by the Kaplan-Meier method and differences in survival were assessed using the log rank method. Comparison between groups was performed using chi square for categorical variables or Kruskal Wallis test for continuous variables. Potential associations between pre- and intra-operative factors, as well as histological outcome and tumour recurrence were tested using univariate logistic regression for continuous variables or chi-square for discrete variables test at the level of $P<0.25$[229]. Significant variables in the univariate analysis were included in the multivariate logistic regression

model and were considered to be significant if $P<0.05$. Univariate and multivariate analyses were carried out using the statistical package R 2.1.14[230]. Ethical approval for the study was obtained from the South West Health Research Authority. Formal Research Ethics Committee review was not required because patient data were collected during their normal hospital care and were anonymised for research purposes. No patient consent was required for this study.

4.4 Results

During the study period 164 liver resections were performed for CRLM in 160 patients who did not receive pre-resection liver-directed chemotherapy. In seven cases, no preoperative imaging was available, leaving 157 resections for analysis, including 79 (50.3%) major and 78 (49.7%) minor resections. Details of patients undergoing surgery are displayed in Table 4.1.

N=157		Median (Range)	Count (%)	Tumour doubling time (days)	Pearson's correlation coefficient	P-Value
Age		69 (34-90)			-0.041	0.613
Gender	Female		52 (33.1)	45 (-398 to +1081)		0.632
	Male		105 (66.9)	48 (-743 to +803)		
T stage of primary	0		1 (0.6)	231		0.035*
	1		6 (3.8)	119 (69 to 190)		
	2		10 (6.4)	40 (-166 to +278)		
	3		96 (61.1)	47 (-493 to +511)		
	4		38 (24.2)	44 (-743 to +1081)		
	Not available		6 (3.8)			
N stage of primary	0		79 (50.3)	45 (-602 to +511)		0.070
	1		49 (31.2)	58 (-509 to +1081)		
	2		25 (15.9)	35 (-743 to +803)		
	Not available		4 (2.5)			
V stage of primary	0		78 (49.7)	45 (-743 to +803)		0.215
	1		41 (26.1)	49 (-167 to +1081)		
	Not available		38 (24.2)			
Duke's Stage of primary	A		11 (7.0)	73 (-52 to +231)		0.054
	B		65 (41.4)	44 (-603 to 511)		
	C		77 (49.0)	48 (-743 to +1081)		
	Not available		10 (6.4)			
Apical node status of primary	Positive		13 (8.3)	34 (-166 to +803)		0.284
	Negative		121 (77.1)	47 (-743 to +511)		
	Not available		23 (14.6)			
Differentiation of primary	Well/moderate		39 (24.8)	51 (-493 to +803)		0.462
	Moderate		59 (37.6)	46 (-509 to + 511)		
	Moderate/poor		4 (2.5)	32 (-743 to +44)		
	Poor		8 (5.1)	34 (-167 to +169)		
	Not available		47 (29.9)			
Site of primary	Colonic		74 (47.1)	47 (-743 to +803)		0.613
	Rectal		83 (52.9)	48 (-493 to +1081)		
Timing of liver metastases	Synchronous		28 (17.8)	38 (-336 to +189)		0.444
	Metachronous		129 (82.2)	48 (-743 to +1081)		
Previous adjuvant chemotherapy	Yes		66 (42.0)	48 (-743 to +803)		0.979
	No		91 (58.0)	44 (-603 to +1081)		
Repeat operation	Yes		23 (14.6)	33 (-743 to +1081)		0.050*
	No		134 (85.4)	49 (-603 to +803)		
Number of liver lesions		1 (1-9)			-0.051	0.529
Diameter of largest metastasis at diagnosis (mm)		25 (5-110)			0.019	0.816
Differentiation of liver metastases	Well		1 (0.6)	69		0.768
	Well/moderate		33 (21.0)	54 (-202 to +278)		
	Moderate		77 (49.0)	43 (-743 to +1081)		
	Moderate/poor		1 (0.6)	60		
	Poor		2 (1.3)	145 (+10 to +280)		
	Not stated		43 (27.4)	48 (-603 to +803)		
Vascular invasion of liver metastases (microscopic)	Yes		28 (17.8)	45 (-603 to +189)		0.715
	No		129 (82.2)	47 (-743 to +1081)		

Table 4.1 Characteristics of 157 patients undergoing resection for CRLM showing tumour doubling time in subsets. *Significant at P<0.05

In sixty-six cases (42.0%), patients received adjuvant chemotherapy following primary colorectal surgery, of whom 19 (28.8%) were treated with 5-FU, 18 (27.3%) with capecitabine, 10 (15.2%) with capecitabine and oxaliplatin, two with capecitabine and bevacizumab and one with 5-FU and oxaliplatin. Details of the post-primary surgery adjuvant regime were not available in 16 patients (25%). The median number of cycles of adjuvant chemotherapy was six (1-8). The median interval between primary colorectal resection and the diagnosis of metachronous tumours was 15 months (3 months – 7.9 years).

The median interval from diagnosis of CRLM to liver resection was 99 days (20-548 days). CRLM were diagnosed by MRI in one patient and by CT in 156 patients (99%). The median diameter of the largest tumour was 25mm (5-110) at diagnosis and 35mm (3-155) in the resection specimen ($P<0.001$). The median change in diameter during this interval was +38% (-92% to +518%) and the median rate of increase in maximum tumour diameter was 2.92% per week (-7.0% to +37.7%) (Figure 4.1). In 27 patients (17.2%) the maximum tumour diameter in the resection specimen was smaller than that determined by pre-operative imaging. The median calculated tumour DT was 47 days (-743 to 1081 days).

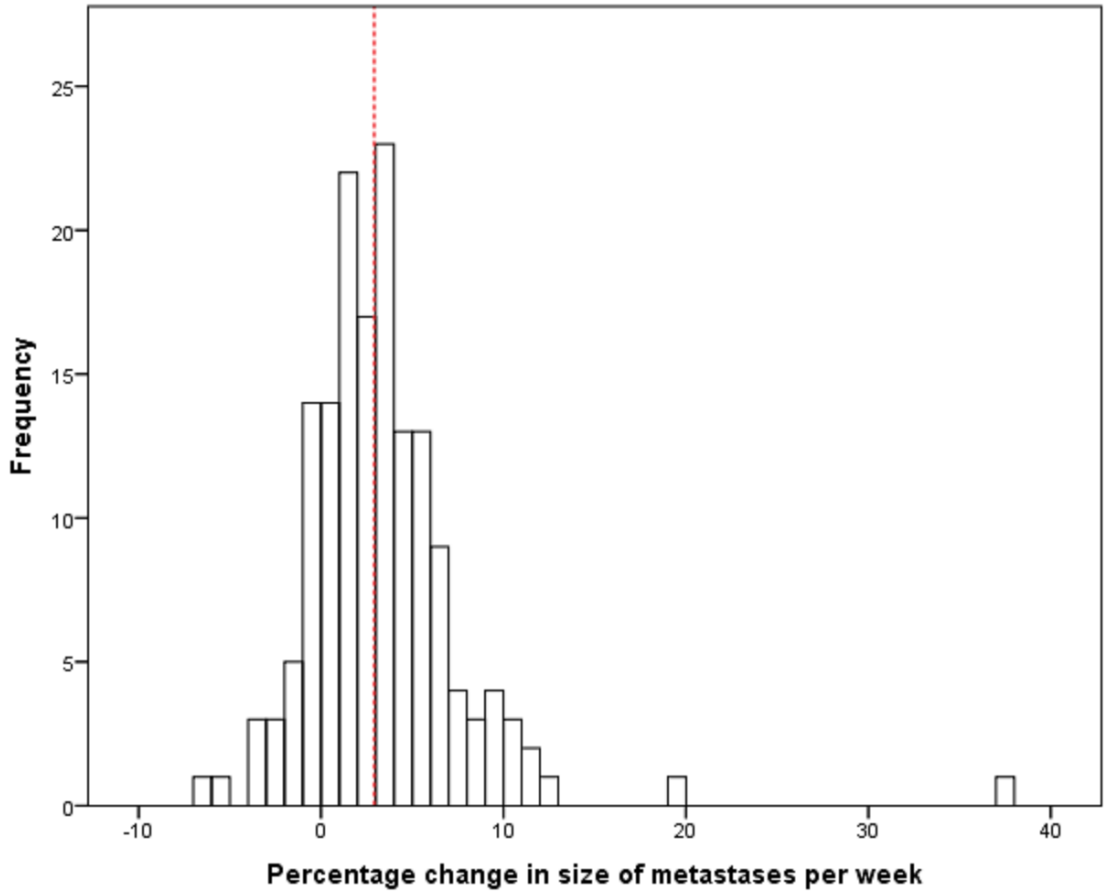


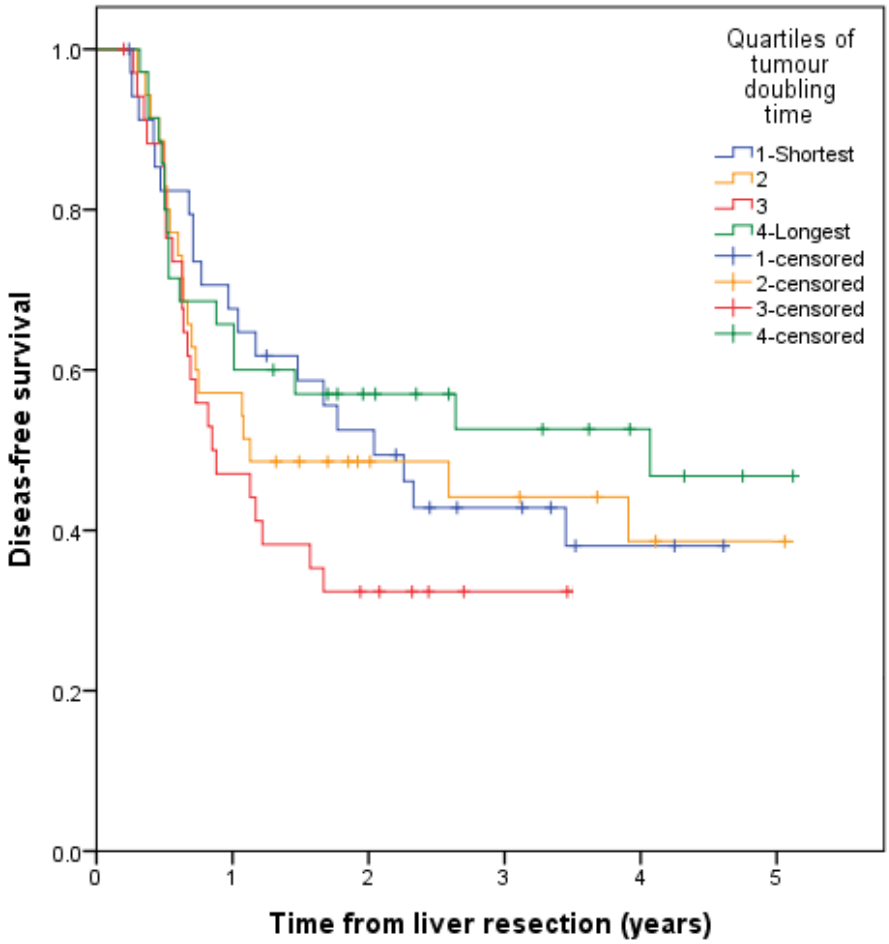
Figure 4.1 Rate of change in tumour size from diagnosis to resection in 157 patients with colorectal liver metastases

Median change in size = +2.9% per week (-7.0% to +37.7%).

Assessment of potential associations between tumour DT and other patient factors revealed an association with primary tumour stage (P=0.035). The median tumour DT was longer in patients with T1 tumours (119 days) compared to those with T2 (40 days), T3 (47 days) and T4 (44 days) tumours. Tumour DT was shorter in patients undergoing repeat liver resection (33 vs. 49 days) (Table 4.1).

Seventeen patients were excluded from survival analysis because they underwent non-curative resection (n=7), developed cut surface recurrence after

an R1 resection (n=3) or did not undergo surveillance imaging (n=7), leaving 140 patients for analysis. At closure of the study the median follow-up was 1.2 years (0.2-7.3). Eighty-one patients (57.9%) suffered tumour recurrence within the study period, and there were 48 deaths (34.3%). The median disease-free survival of the group was 1.57 years. Analysis of quartiles determined by tumour DT prior to surgery revealed that DT was not associated with disease-free survival after surgery (P=0.182) (Figure 4.2).



Quartile 1 Shortest						
Number at risk	35	23	17	11	7	
Number of events		11	5	3	1	
Quartile 2						
Number at risk	35	20	12	10	7	6
Number of events		15	3	1	1	0
Quartile 3						
Number at risk	35	16	10	6		
Number of events		18	5	0		
Quartile 4 Longest						
Number at risk	35	23	16	12	9	6
Number of events		12	3	1	0	1

Figure 4.2 Kaplan–Meier disease-free survival curves according to tumour doubling time quartiles among 140 patients with CRLM not treated with liver-directed chemotherapy (Log rank P=0.309)

Multivariate analysis of pre-operative factors including rate of growth of CRLM revealed that the only significant predictor of tumour recurrence was the number of metastases resected (Table 4.2). For each extra metastasis, the risk of recurrence increased by a factor of 1.3 (P=0.013). Tumour DT was not found to be an independent predictor of tumour recurrence (P=0.593).

Table 4.2 Univariate and multivariate analysis of factors associated with tumour recurrence following liver resection for CRLM in 140 patients not treated with liver-directed chemotherapy

N=140		Not recurred (n=59)		Recurred (n=81)		Univariate		Multivariate analysis	
		Median (range)	Count (%)	Median (range)	Count (%)	P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)
Age		69 (51-84)		68 (34-87)		0.786			
Gender	Male		43 (72.9)		53 (65.4)	0.349			
	Female		16 (27.1)		28 (34.6)				
T stage of primary	0		1 (1.7)		0	0.560			
	1		0		5 (6.2)				
	2		4 (6.8)		6 (7.4)				
	3		35 (59.3)		48 (59.3)				
	4		17 (28.8)		19 (23.5)				
	NA		2 (3.4)		3 (3.7)				
N stage of primary	0		29 (49.2)		42 (51.9)	0.635			
	1		21 (35.6)		23 (28.4)				
	2		8 (13.6)		14 (17.3)				
	NA		1 (1.7)		2 (2.5)				
V stage of primary	0		26 (44.1)		46 (56.8)	0.133*		0.203	0.52 (0.19-1.42)
	1		18 (30.5)		17 (21.0)				
	NA		15 (25.4)		18 (22.2)				
Duke's Stage of primary	A		4 (6.8)		6 (7.4)	1.000			
	B		24 (40.7)		34 (42.0)				
	C		29 (49.2)		39 (48.1)				
	NA		2 (3.4))		2 (2.5)				
Apical node of primary	Positive		3 (5.1)		9 (15.3)	0.313			
	Negative		43 (72.9)		64 (79.0)				
	NA		13 (22.0)		8 (9.9)				
Site of primary	Colon		29 (49.2)		36 (44.4)	0.704			
	Rectum		30 (50.8)		45 (55.6)				
Timing of metastases	Syn		8 (13.6)		16 (19.8)	0.339			
	Met		51 (86.4)		65 (80.2)				
Previous adjuvant chemotherapy			25 (42.4)		34 (42.0)	0.962			

Table 4.2 continued.

N=140		Not recurred (n=59)		Recurred (n=81)		Univariate		Multivariate analysis	
		Median (range)	Count (%)	Median (range)	Count (%)	P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)
Repeat operation			9 (15.3)		11 (13.6)	0.780			
Wedge resection included			22 (37.3)		33 (40.7)	0.812			
Radiofrequency ablation included			1 (1.7)		1 (1.2)	0.821			
Tumour doubling time (DT)		47.4 (-743 to +1081)		47.6 (-602 to +803)		0.957	0.98 (0.50-1.94)		
Number of liver lesions		1 (1-3)		1 (1-9)		0.073*	1.54 (0.96-2.46)	0.013**	1.30 (1.06-1.59)
Diameter of largest metastasis at diagnosis (mm)		35 (8-155)		40 (3-120)		0.202*	1.01 (1.00-1.02)	0.854	1.00 (0.98-1.02)
Positive resection margin (R1)			10 (16.9)		12 (14.8)	0.699			
Differentiation of liver metastases	Well/mod		10 (16.9)		15 (19.8)	0.801			
	Mod		33 (55.9)		38 (46.9)				
	Mod/poor		0		1 (1.2)				
	Poor		0		2 (2.5)				
	Not stated		16 (27.1)		24 (29.6)				
Vascular invasion of liver metastases (microscopic)	Yes		8 (13.6)		15 (18.5)	0.495			
	No		51 (86.4)		66 (81.5)				

NA = no data available

**** Significant at the level of 0.25 for univariate analysis and included in multivariate analysis***

*****Significant at the level of 0.05 for multivariate analysis***

4.5 Discussion

Despite the wealth of information relating to prognostic factors which affect survival after resection of CRLM the lack of data relating to tumour DT is surprising. Tumour DT has been shown to be a significant prognostic factor in the treatment of many solid tumours in including hepatocellular carcinoma[102], sarcoma[103], renal cancer[104], lung cancer[105] and gynaecological cancer[106]. A study estimating the rate of growth of CRLM used early CT scans in patients not undergoing treatment and found a DT of 112 days[244]. More recently DT of CRLM was estimated by serial scans prior to resection in eight patients and a median DT of 63 days was found[245]. Tumour DT was found to be associated with poorer survival after resection. Estimates of DT of CRLM have also been made by measuring the rise in CEA concentration[245–247], which have revealed a DT of 10-411 days[245,247]. The tumour DT determined by CEA was found to be the most significant marker of outcome following resection in 144 patients[246]. A correlation of increasing CEA secretion with tumour growth has been demonstrated only in animal studies[248], and many CRLM do not secrete the marker[23]. Estimation of DT in pulmonary CR metastases is commonly performed, as serial imaging is frequently undertaken in this situation. The range of DT has been reported as 29-385 days[250,251] and a tumour DT of less than 100 days has been shown to be associated with increased risk of intrapulmonary recurrence following lung resection[252]. Other studies have shown the difficulty of estimating DT in primary colorectal cancer based on changes in tumour size[253].

The main finding of clinical significance from this study is that, in contrast to the treatment of many other solid tumours, and colorectal metastases in the lung,

the rate of growth of CRLM has no influence on survival after resection. The proportion of patients with CRLM who are offered liver resection is small (10-20%)[254,255] and patients undergo a selection process before being offered liver resection. In the majority of cases this involves exclusion of patients with extra-hepatic disease, rapidly progressive disease and where there is extensive replacement of the liver with tumour. Furthermore, this selection process may have involved a 'trial of time' in the early part of this study, which may account for the relatively long interval between diagnosis of liver metastases and liver resection. It is likely that this selection process retains a subset of patients with low-volume, liver-only metastases, whose disease remains temporarily localised to the liver. This finding supports the view that the liver provides a special site of containment of metastatic disease in some patients, in whom surgical resection is likely to be effective[256]. Studies of genetic biomarkers and apoptosis have also revealed that CRLM generally have lower rates of cellular proliferation than primary colorectal cancer[257,258].

A weakness of the study is the comparison of tumour diameter measured radiologically with pathological findings. This method may be subject to error as the accuracy of CT scan in determining diameter of CRLM has not been demonstrated. Correlation of CT measurement with pathological findings has been performed for hepatoma, and CT scans have been shown to overestimate the size of these lesions[259]. The tumour margin of CRLM may be infiltrative and less clearly defined than that of hepatoma[260,261], although some lesions have a clearly defined capsular margin[262]. A degree of subjectivity may be necessary in undertaking a comparison of radiological and pathological findings and it is possible that CT scans underestimate the size of CRLM, which may account for

some of the difference in size seen between imaging and pathological examination. Measurement of a single tumour diameter is however a valid technique and has been shown to correlate well with tumour volume[263]. The large change in tumour diameter (38%) over a long time period (99 days) and the normal appearance of the frequency distribution of changes in diameter in our study however support the validity of the method. Survival after liver resection may be affected by further chemotherapy, and details of chemotherapy administered to patients between liver resection and death are not available, as this treatment may have been administered in other centres. The rate of growth of tumours prior to resection is however not measured in this unit and this feature is unlikely to have led to bias by influencing oncologists in the administration of chemotherapy. Adjuvant chemotherapy following liver resection is also unlikely to have been administered to this patient group as it is not included in our local protocol for the treatment of CRLM without a trial of liver-directed neo-adjuvant treatment.

Although resection for CRLM is mainly offered to patients with disease confined to the liver, tumour recurrence occurs in the majority. Attempts to predict outcome based on morphological characteristics of the liver metastases have met with limited success as they rely on these characteristics being a surrogate for biological behaviour and metastatic potential. Few studies have been undertaken to correlate tumour characteristics with biological markers of aggressiveness, although a long tumour DT has been shown to be associated with a favourable host immune response[245].

This study reveals that among selected patients with liver-only disease the rate of tumour growth of CRLM prior to surgery does not influence post-operative

survival, and should not be regarded as an adverse factor when considering the role of liver resection in this patient group. Clinicians should take this into consideration when discussing patients at MDT and deciding on further management. Furthermore, clinicians can use this evidence to counsel patients preoperatively who may be concerned regarding the increase in size of liver metastases whilst awaiting surgery.

Chapter 5 : Rebound growth of hepatic colorectal metastases after neo-adjuvant chemotherapy: effect on survival after resection

Lim E*, Wiggans MG*, Shahtahmassebi G, Aroori S, Bowles MJ, Briggs CD, Stell DA (2016) Rebound growth of hepatic colorectal metastases after neo-adjuvant chemotherapy: effect on survival after resection – accepted for publication in HPB (Oxford) 18(7) 586-92 (*Joint 1st authors)

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5.1 Abstract

Introduction

A period of recovery is commonly allowed between completion of chemotherapy for colorectal liver metastases (CRLM) and resection, during which tumour progression may occur. The study-aim is to assess the growth of CRLM in this interval and association with outcome.

Methods

Data on 146 patients were analysed. Change in tumour size was assessed by comparing size determined by imaging performed on completion of chemotherapy with that determined by examination of the resected specimen, categorised by RECIST criteria.

Results

In the interval before surgery sixteen patients (11%) fulfilled criteria for partial response (PR), 48 (33%) had stable disease (SD) and 82 (56%) had progressive disease (PD). Among patients with PD following chemotherapy the median disease-free survival of patients who initially responded (26 months) was longer than in those who initially had stable disease (7 months) (P=0.002).

No association was noted between rate of tumour growth after completion of chemotherapy and disease-free survival.

Discussion

Change in tumour size after completion of chemotherapy is variable and can be rapid, especially in patients who initially respond to treatment. However, disease-free survival is determined by tumour behaviour during treatment and not by change in size after completion of chemotherapy.

5.2 Introduction

Liver resection provides a potential cure for patients with colorectal liver metastases (CRLM), with five-year survival rates ranging from 32-65%[41]. Neo-adjuvant systemic chemotherapy has been advocated in patients with initially resectable[92,264] and unresectable[265–267] CRLM. Tumour response to chemotherapy is usually assessed by imaging techniques performed before and after treatment and some studies have suggested that surgery should not be performed when progression on chemotherapy occurs, as the outcome is poor[268,269]. Although the proportion of patients with CRLM who respond to liver directed chemotherapy (LDC) has been defined in many studies[92,94] the duration over which the changes are sustained following completion of treatment has not been described, and the consequences of tumour progression in the interval between completion of chemotherapy and surgery are unknown. As chemotherapy can cause significant hepatotoxicity[197,270] it is common practice to allow a chemotherapy-free interval for these changes to reverse before undertaking liver resection[196], potentially allowing uninhibited tumour progression. The aim of this study was to assess the change in size of

CRLM between post-chemotherapy imaging and liver resection and to measure potential associations of this change with tumour recurrence and survival.

5.3 Methods

Analysis of data retrieved from a database of all patients undergoing liver resection for CRLM between May 2004 and December 2012 was performed. Systemic chemotherapy was administered to patients with radiological evidence of CRLM, where liver resection was planned, according to local protocols. The diameter of the largest metastasis was measured by CT scan and response to chemotherapy graded by RECIST criteria[271]. Any further change in tumour size between completion of chemotherapy and liver resection was measured by comparing the maximum diameter of lesions determined by post-chemotherapy imaging and the maximum diameter determined by examination of the resected specimen, expressed as a function of time. Time intervals are expressed in weeks with inter-quartile range (IQR). For purposes of comparison changes in size during this interval were also graded by RECIST criteria. Tumour doubling-time (DT) was calculated using the equation

$$DT=Ti \times Log2 / (3 \times Log(Dp/Dr)$$

where Ti = time interval between post-chemotherapy imaging and surgery, Dp = diameter at pathology and Dr = diameter measured by imaging[107].

Data relating to primary tumour pathology, the use of adjuvant chemotherapy for primary colorectal cancer, systemic chemotherapy administered for CRLM and other clinical information were retrieved. Synchronous metastases were defined as those diagnosed prior to, or within two months of primary surgery.

Liver resections were described according to the Brisbane classification[272] and undertaken using standard techniques.

Post-operative follow-up included surveillance CT scans performed at six-monthly intervals for three years and annually to five years after resection. The timing and site of tumour recurrence were recorded as well as dates of death. Follow-up was completed at March 2014.

Patients were excluded from disease-free survival analysis if they died without undergoing surveillance imaging, or underwent planned non-curative resections. Patients who developed resection-margin recurrence following a resection with margin-involvement (R1) were also excluded as these were deemed to have been due to technical failure rather than tumour recurrence.

Survival curves were constructed by the Kaplan-Meier method and differences in survival assessed using the log rank method. Comparison between groups was performed using chi square for discrete variables and Mann Whitney U test for continuous variables. In survival analyses patients who suffered PD after completion of chemotherapy were split into quartiles according to the rate of increase in size of the largest tumour.

Ethical approval for the study was obtained from the South West Health Research Authority. Formal Research Ethics Committee review was not required because patient data were collected in the course of normal hospital care and were anonymised for research purposes.

5.4 Results

During the study period 155 patients were treated with neo-adjuvant chemotherapy prior to liver resection. Details of patients undergoing surgery are shown in Table 5.1 and details of chemotherapy regimes in Table 5.2.

N=155		**Median (Range)**	**Count (%)**
Age		65 (33-83)	
Gender	Female		67 (43.2)
	Male		88 (56.8)
Timing of liver metastases	Synchronous		120 (77.4)
	Metachronous		35 (22.6)
Previous adjuvant chemotherapy	Yes		23 (14.8)
	No		132 (85.2)
Repeat operation	Yes		5 (3.2)
	No		150 (96.8)
Number of liver lesions		2 (0-10)	
Diameter of largest metastasis at diagnosis (mm)		25 (6-130)	

Table 5.1 Characteristics of 155 consecutive patients undergoing resection for colorectal liver metastases after receiving systemic chemotherapy

N=155			Count (%)
Chemotherapy regime	Oxaliplatin and capecitabine		118 (76.1)
	5-FU alone		1 (0.6)
	Oxaliplatin and 5-FU		15 (9.7)
	Irinotecan		6 (3.9)
	Capecitabine alone		11 (7.1)
	Notes unavailable		4 (2.6)
	Number of cycles		4 (1-18)
Biological agent	Yes	Cetuximab	7 (4.5)
		Bevacizumab	2 (1.3)
	No		142 (91.6)
	Unknown		4 (2.6)
Dose reduction	Yes		21 (13.5)
	No		134 (86.5)
Change in size of largest tumour on imaging according to RECIST	Complete or partial response		72 (46.5)
	Stable disease		48 (31.0)
	Progressive disease		26 (16.8)
	No imaging available		9 (5.8)

Table 5.2 Systemic chemotherapy regimens and response to treatment for 155 patients undergoing liver resection for colorectal liver metastases

The median number of cycles of chemotherapy administered was 4 (IQR 4-6). Three patients received second-line chemotherapy. Nine patients were excluded from response analysis because imaging was not available, leaving 146 patients. The median interval between pre- and post-chemotherapy scans in patients was 15.3 weeks (IQR 12.0-20.4 weeks) and the median change in diameter of the largest liver metastases during this period was a reduction of 24% (-100% to +342%), or -1.3% (-9.6% to +12.6%) per week. Sixty-four patients (43.8%) fulfilled the RECIST criteria for partial response (PR) and eight patients (5.4%) had a complete response to treatment. Forty-eight patients (32.8%) had stable disease (SD) and twenty-six patients (17.8%) suffered

progressive disease (PD). The median reduction in tumour size in patients who responded to treatment was -3.2% (-9.6% to -0.9%) per week.

The median interval between post-chemotherapy imaging and liver resection was 10.4 weeks (7.1-17.6 weeks), and was similar across patient groups regardless of response to chemotherapy (Table 5.3).

Initial response (n=146)		**Complete or partial response (>30%) (n=72)**	**Stable disease (n=48)**	**Progressive disease (>20%) (n=26)**	**P-value CR and PR vs PD**
Median interval in weeks from post chemotherapy imaging to liver resection (range)		10 (1-98)	10 (1-54)	10 (1-54)	0.570
Median % change in diameter (range)		+42 (-100 to +838)	+22 (-100 to+157)	+22 (-38 to +156)	<0.001
Change in diameter after completion of chemotherapy (%)	Further Response	7 (9.7)	8 (16.6)	1 (3.8)	0.258
	Stable disease	20 (27.8)	16 (33.3)	12 (46)	
	Progressive disease	45 (62.5)	24 (50)	13 (50)	

Table 5.3 Change in maximum diameter of liver metastases among 146 patients during interval between post-chemotherapy imaging and liver resection, categorised according to initial response

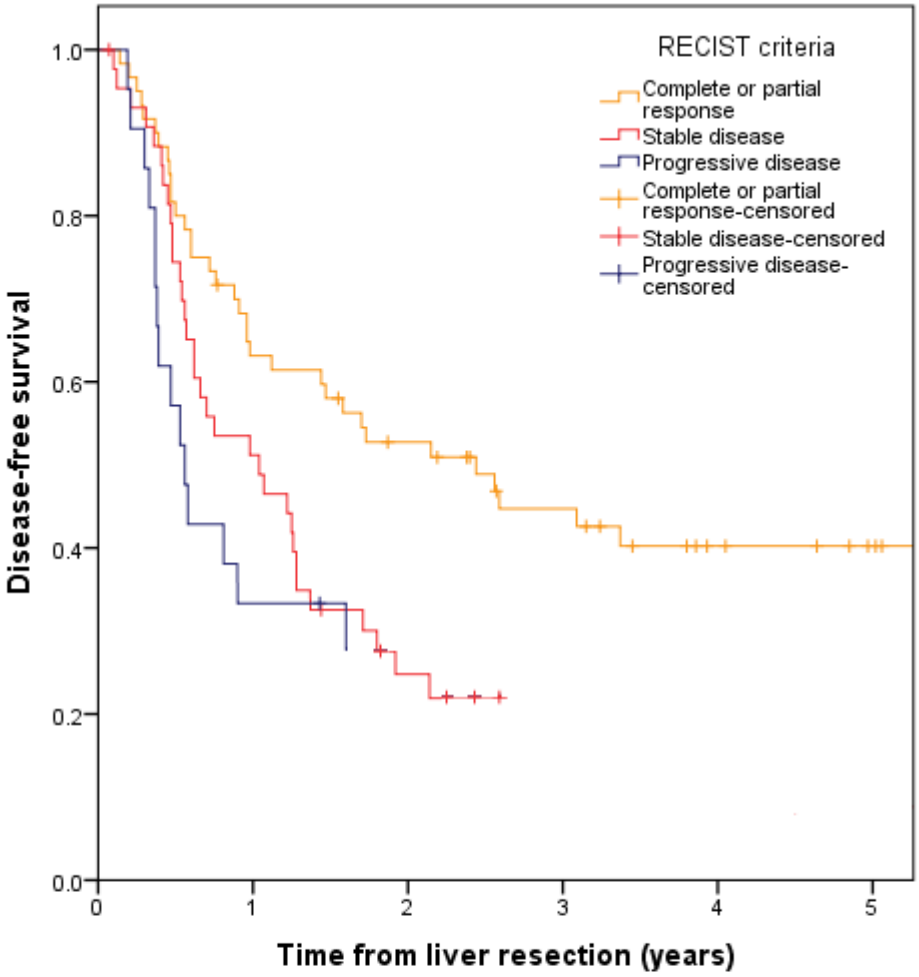
During this period, the largest tumour diameter increased in 102 patients (69.9%) and decreased in 37 (25.3%) with a median change of +2.3% per week (-11.1 to +28.0%). By RECIST criteria 16 patients (10.9%) had PR, 48 patients (32.9%) had SD and 82 patients (56.2%) had PD in the interval before surgery. The increase in tumour diameter was greatest in patients who had a partial or complete response while receiving chemotherapy (Table 5.3). Of the 120 patients who had either PR or SD whilst receiving chemotherapy only 51 (42.5%) remained in either of these two categories whilst awaiting surgery. Thirteen of 26 patients (50%) who suffered PD while receiving chemotherapy

suffered continued disease progression in the interval to surgery (P=0.352), and only one patient had a late response. The rate of change in size of largest tumour during this interval was 2.3% per week, (-11.1 to +28.0%) which was significantly greater than during the treatment interval (-1.3%, -9.6% to +12.6%) (P=0.007). The median doubling time of tumours which increased in size during this period was 45.5 days (0.7-1869).

In survival analysis 11 patients were excluded because surgery was deemed non-curative or a staged resection was not completed, and three patients were excluded because they died without undergoing surveillance imaging. Seven patients were excluded because they developed cut surface recurrence after R1 resection leaving 125 patients for analysis, of whom 104 patients initially had PR or SD. At closure of the study the median follow-up was 36 months (1-97 months). Seventy-nine patients (63.2%) suffered tumour recurrence and there were 45 deaths (36%). Tumour response whilst receiving chemotherapy was associated with significantly longer disease-free survival than PD or SD (Figure 5.1).

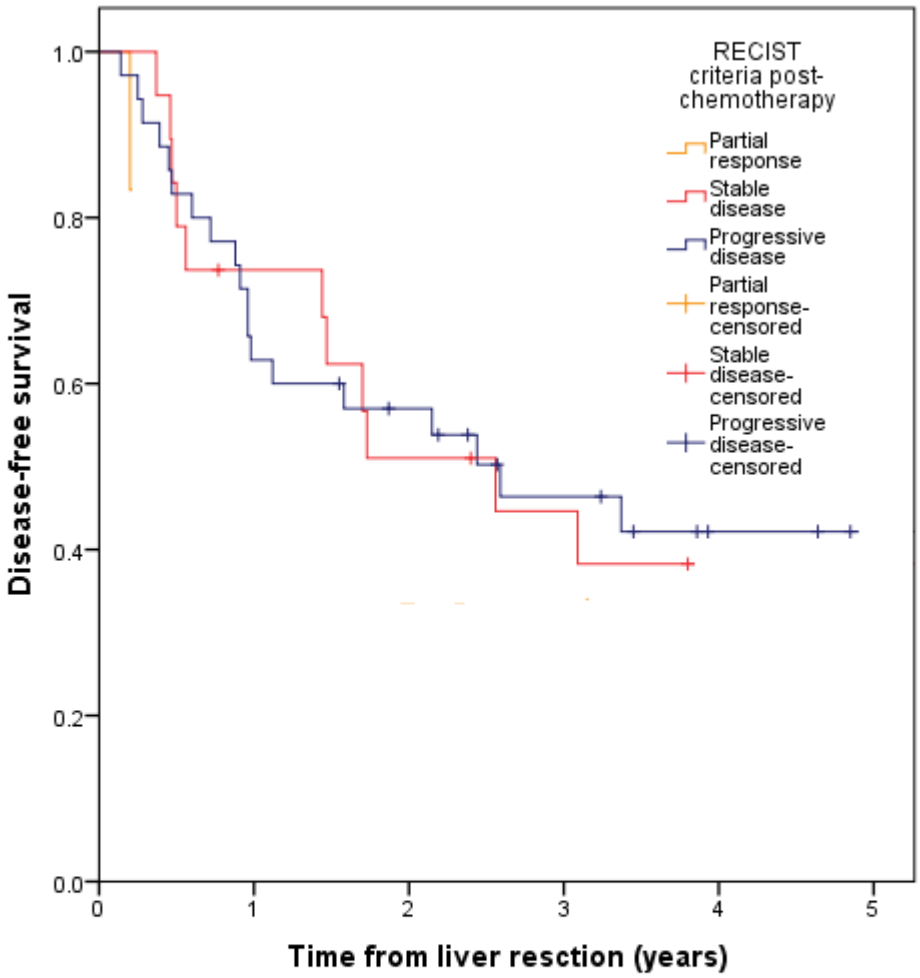
Among the 60 patients who initially responded and the 44 patients who had stable disease whilst receiving chemotherapy disease-free survival was similar regardless of tumour behaviour after completion of treatment (Figure 5.2 and 5.3 respectively). Among the patients who suffered PD in the interval after completing chemotherapy, survival was determined by initial response to treatment. In 35 patients who initially responded the median disease-free survival was 26 months (range 2-84) compared to seven months (range 1-54) in 22 patients who initially had stable disease (P=0.002). Among the total group of 66 patients who suffered PD after completion of chemotherapy in whom survival

analysis was undertaken the rate of increase in size of largest tumour was not associated with disease-free survival (Figure 5.4).



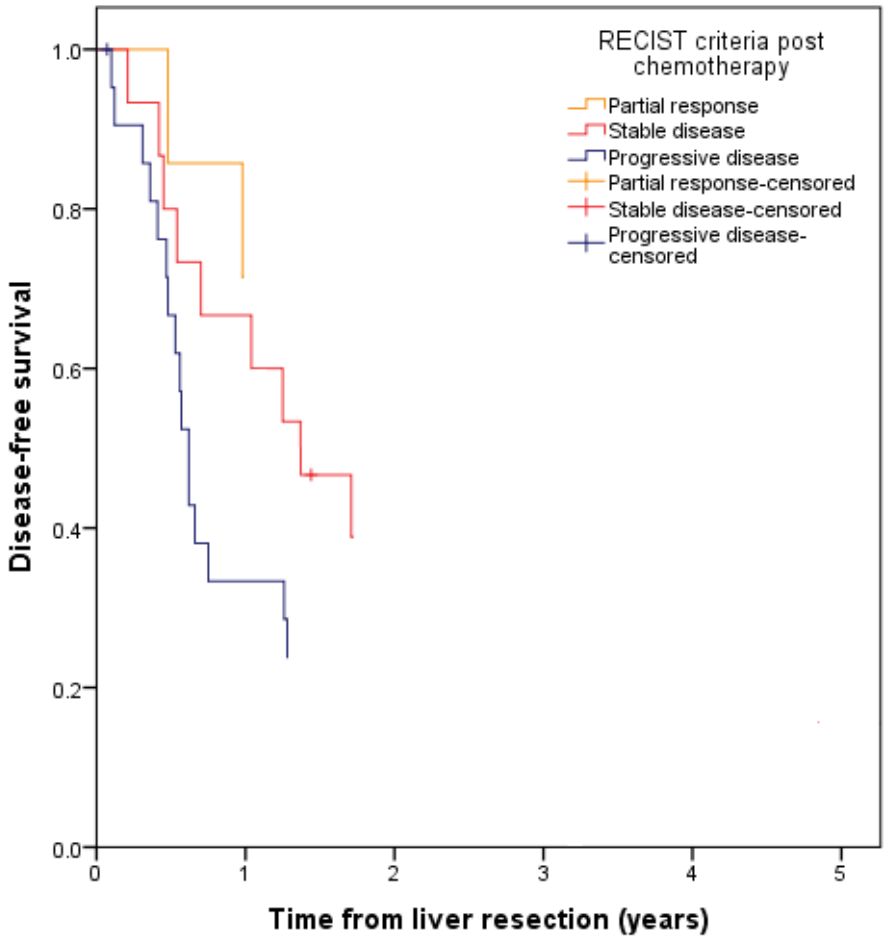
Complete or partial response					
Number at risk	60	37	26	19	11
Number of events		21	6	4	2
Stable disease					
Number at risk	44	21	8		
Number of events		19	9		
Progressive disease					
Number at risk	21	6			
Number of events		14			

Figure 5.1 Kaplan–Meier disease-free survival curves following liver resection for colorectal liver metastases for 125 patients treated with preoperative systemic chemotherapy, determined by response to treatment (Log rank P=0.003)



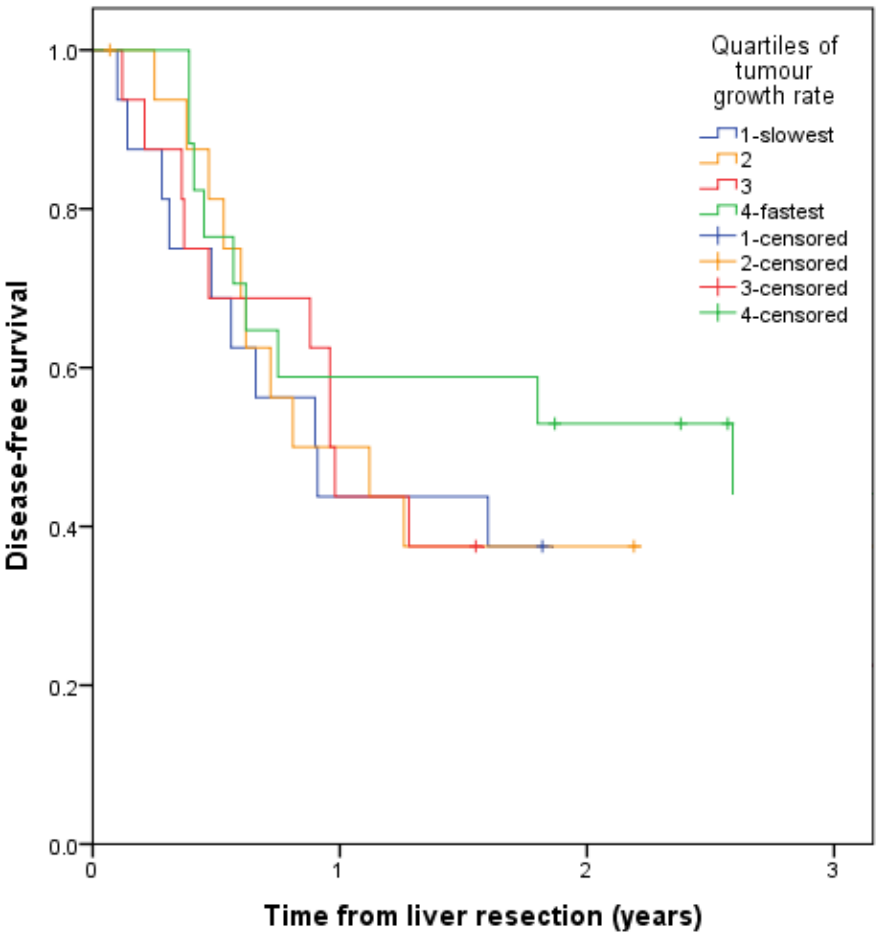
Partial response						
Number at risk	6					
Number of events						
Stable disease						
Number at risk	19	13	9	7	5	
Number of events		5	4	1	1	
Progressive disease						
Number at risk	35	22	18	12	7	5
Number of events		13	2	3	1	0

Figure 5.2 Kaplan–Meier disease-free survival curves following liver resection for colorectal liver metastases for 60 patients who initially had partial or complete response to chemotherapy categorised according to tumour behaviour after completion of chemotherapy (PR/SD/PD) (P=0.591)



Partial response		
Number at risk	7	5
Number of events		2
Stable disease		
Number at risk	15	10
Number of events		5
Progressive disease		
Number at risk	22	7
Number of events		14

Figure 5.3 Kaplan–Meier disease-free survival curves following liver resection for colorectal liver metastases for 44 patients who initially had stable disease categorised according to tumour behaviour after completion of chemotherapy (PR/SD/PD) (P=0.436)



Quartile 1 - slowest				
Number at risk	16	7		
Number of events		9		
Quartile 2				
Number at risk	17	8	6	
Number of events		8	2	
Quartile 3				
Number at risk	16	7		
Number of events		9		
Quartile 4 - fastest				
Number at risk	17	10	8	5
Number of events		7	1	1

Figure 5.4 Kaplan–Meier disease-free survival curves following liver resection for colorectal liver metastases for 66 patients who suffered tumour progression (PD) after completion of chemotherapy, divided into quartiles according to rate of tumour growth (P=0.556)

5.5 Discussion

The principle findings of this study are that:

a) tumour response to chemotherapy is associated with improved disease-free survival after resection of CRLM
b) in a large proportion of these patients the treatment effect is transient and disease progression occurs rapidly after stopping therapy
c) the change in tumour size is more rapid after completion of chemotherapy than during treatment
d) relative change in tumour size after completion of chemotherapy is not associated with disease-free survival

Although a regime of six cycles of oxaliplatin and capecitabine has recommended as a neoadjuvant chemotherapy treatment prior to liver resection[92], the most common regime adopted in this series was four cycles. This regime has been used to minimise complications due to hepatotoxicity which can occur following use of these agents[197]. The association of response to neo-adjuvant chemotherapy estimated by RECIST criteria with improved disease-free survival compared to progressive disease has been shown previously[268,269,273], though others have shown no independent association[94].

In keeping with other units, a period of recovery after completion of chemotherapy is allowed to minimise the risks of hepatotoxicity. The optimum period of recovery has not been defined but four weeks has been recommended based on studies of the recovery of hepatic clearance of indocyanine green[274]. In the present study, the median interval between completion of chemotherapy and surgery was 10 weeks. This period includes

the time needed for notification of completion of chemotherapy, MDT discussion, clinic appointments and preparation for surgery. No previous study has addressed the change in tumour size during this period and potential associations with outcomes for patients after surgery. The majority of patients who initially responded to chemotherapy or had stable disease will suffer disease progression after completion of chemotherapy. For tumours which increase in size in this interval the rate of tumour growth is very rapid (2.3% per week), with a calculated tumour DT of 46 days. The DT of untreated CRLM has been reported previously as between 63 and112 days[244,245]. This rapid tumour growth does not however appear to influence disease-free survival after resection which is determined by the initial response to chemotherapy. Among the group of patients who suffer disease progression in the interval to surgery the median disease-free survival of patients who initially responded (26 months), is greater than that of patients who initially had stable disease (7 months) (P=0.002).

The lack of effect of rebound growth in tumour size after completion of chemotherapy is unusual in the context of the expected behaviour of solid tumours. There is evidence that rapid tumour proliferation is associated with poor outcome in colorectal cancer, although these studies have usually employed molecular kinetic markers[275–277]. Despite these findings there is little evidence that in vitro markers of tumour proliferation correlate with macroscopic tumour growth or that the growth rate of CRLM correlates with poor outcome after resection. It is possible that the increase in tumour size noted after cessation of chemotherapy represents tumour swelling, rather than growth of viable tumour cells, and tumour expansion may be associated with cell death[278].

The change in size of CRLM may also not be representative of extra-hepatic effects. Tumour recurrence after resection of CRLM is caused by micro-metastases not detected at the time of initial treatment[279,280], and response to treatment of these malignant cells may be more sustained than that by large liver metastases. In this context change in size of CRLM can be seen as a surrogate marker for the effects of chemotherapy on peripheral micrometastases only during treatment. Decrease in size of these lesions may indicate a beneficial effect in terms of micrometastatic disease, whereas rebound growth after cessation of treatment may not indicate recovery of peripheral micrometastases.

An important question raised by these findings relates to the length of time allowed between completion of chemotherapy and liver resection. No trial has been undertaken to address this issue and the risks are not uniform between patients, being affected by the extent of the planned resection and the size of the future liver remnant. Our findings suggest that when chemotherapy is administered to patients with resectable tumours, disease progression after cessation of chemotherapy has no adverse effect on outcome and should not influence the timing of surgery. When chemotherapy is used specifically to down-size CRLM of borderline resectability however, rapid tumour progression after cessation of treatment may render the lesions unresectable, and earlier liver resection may be desirable in this group.

The potential weakness of this study relates to the measurement of tumour size. We have compared the maximum tumour diameter measured by imaging with that noted on macroscopic measurement of the resection specimen using a unidimensional measurement, as this has been shown to be representative of

tumour volume[263]. This method has not however been previously validated by a direct comparison of the assessment of tumour size by imaging and pathology, and no data is available regarding the accuracy of CT scans in determining the size of CRLM. CT scan measurements however have been shown to be accurate in the measurement of hepatoma[281]. Also, the time point at which post-chemotherapy imaging was undertaken was variable, and some change in size may have occurred in the interval between completion of chemotherapy and final imaging. Another potential source of inaccuracy is that data relating to the use of chemotherapy after surgery was not included in survival analyses. Uptake of adjuvant chemotherapy after liver resection is generally poor, though many patients will have received palliative treatment. Measurement of tumour growth after completion of chemotherapy is not undertaken in clinical practice and this factor is unlikely to have led to bias in the administration of chemotherapy to individual patients. The sample size used in this study is not large, and a study with greater power may reveal differences in survival between groups not apparent in this analysis.

5.6 Conclusion

Change in tumour size after completion of chemotherapy is variable and can be rapid, especially in patients who initially responded to treatment. It does not appear to affect outcome and should not be considered an adverse factor when counselling patients or determining treatment options. Clinicians should be aware of these findings when discussing patients at MDTs and use them to guide decision making.

Chapter 6 : The interaction between diabetes, body mass index, hepatic steatosis and risk of liver resection: insulin dependent diabetes is the greatest risk for major complications.

Wiggans MG, Lordan JT, Shahtahmassebi G, Aroori S, Bowles MJ, Stell D A. (2014) The interaction between diabetes, body mass index, hepatic steatosis, and risk of liver resection: Insulin dependent diabetes is the greatest risk for major complications. *HPB Surg* 2014: 586159.

DOI:10.1155/2014/586159

6.1 Abstract

Introduction

This study aimed to assess the relationship between diabetes, obesity and hepatic steatosis in patients undergoing liver resection and to determine if these factors are independent predictors of major complications.

Methods

Analysis of a prospectively maintained database of patients undergoing liver resection between 2005 and 2012 was undertaken. Background liver was assessed for steatosis and classified as <33% and ≥33%. Major complications were defined as Grade III-V complications using the Dindo-Clavien classification.

Results

504 patients underwent liver resection, of whom 56 had diabetes and 61 had steatosis ≥33%. Median BMI was 26 kg/m^2 (16-54 kg/m^2). 94 patients

developed a major complication (18.7%). BMI ≥ 25 kg/m^2 (P = 0.001) and diabetes (P = 0.018) were associated with steatosis ≥33% Only insulin dependent diabetes was a risk factor for major complications (P = 0.028). Age, male gender, hypoalbuminaemia, synchronous bowel procedures, extent of resection and blood transfusion were also independent risk factors.

Conclusions: Liver surgery in the presence of steatosis, elevated BMI, and non-insulin dependent diabetes is not associated with major complications. Although diabetes requiring insulin therapy was a significant risk factor, the major risk factors relate to technical aspects of surgery, particularly synchronous bowel procedures.

6.2 Introduction

Liver failure occurs in up to 32% of patients following liver resection[137,181–183,282] and is a major contributor to both morbidity[63] and mortality[148]. Liver resection is technically more difficult in patients with parenchymal liver disease[283] and the risks of liver resection are increased due to impaired hepatic regeneration[284].

Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of liver disease in the West[110] and is also the commonest cause of a sustained rise in serum transaminases in patients with no history of chronic liver disease[285]. NAFLD encompasses steatosis (excess accumulation of triglycerides), steatohepatitis (hepatocyte damage, inflammatory infiltrate and fibrosis) and cirrhosis[286] and can be demonstrated with routine histological staining. NAFLD is associated with diabetes mellitus and obesity[287,288] which are also undergoing a global epidemic[289,290]. However, not all patients with obesity and

diabetes develop NAFLD and similarly not all patients with NAFLD suffer either diabetes or obesity[291].

Liver-directed chemotherapy is also associated with hepatotoxicity. Steatohepatitis has been shown to occur in 20% of patients who receive irinotecan and 5% of those who receive fluorouracil (5FU)[270], with a resulting increase in complications after surgery. Oxaliplatin is associated with sinusoidal obstruction syndrome[197,270]. Recreational alcohol use is also a major cause of hepatic steatosis[292].

A meta-analysis has shown that hepatic steatosis is associated with increased risk of postoperative complications and that moderate and severe steatosis are associated with increased mortality compared to patients with normal liver parenchyma or mild steatosis[111]. However, this analysis is based on four studies, only two of which included both BMI and diabetes in multivariate analyses[62,184,283,293]. Obesity, diabetes and hepatic steatosis often coexist in the metabolic syndrome[109], and the increased risk of operating in the presence of steatosis may be due to associated co-morbidity. Diabetes mellitus and obesity are independent risk factors for postoperative complications following other types of major surgery, including infectious[112,113,294], cardiovascular[294,295] and renal complications[113,294,295]. Furthermore, in the four studies included in the meta-analysis heterogeneous definitions of post-operative complications were used, and often relatively minor complications included. Recently complications after liver surgery have been classified by the Dindo-Clavien system[296], which stratifies severity of complications and allows comparison of outcomes between centres.

The aim of this study was to assess the relationship between the incidence of diabetes, obesity and hepatic steatosis in patients undergoing liver resection after a period of abstention from alcohol consumption and to determine if these factors are independent predictors of major complications following liver resection, using the Dindo-Clavien system.

6.3 Methods

A retrospective analysis of a prospectively maintained database of all patients undergoing liver resection between July 2005 and September 2012 was undertaken. Patient characteristics, laboratory data and intra-operative details were retrieved. BMI was recorded pre-operatively and the cohort divided into three categories; 18.5-24.99 kg/m^2 (normal), 25-29.99 kg/m^2 (overweight), and ≥30 kg/m^2 (obese). Diabetes was categorised according to the requirement for insulin. The presence of pre-existing chronic liver disease was confirmed by histology. American Association of Anesthesiologists (ASA) grade was determined by the responsible anaesthetist and the physiologic score calculated according to the POSSUM system[297]. Selected patients were treated with neoadjuvant chemotherapy. All patients underwent pre-operative counselling by a nurse specialist where abstention from alcohol was mandated. This instruction was also contained in a patient information sheet. The normal interval from pre-operative counselling to surgery in our series is approximately 30 days.

Liver resections were defined according to the Brisbane classification[17] and undertaken using standard techniques, using hepatic inflow occlusion selectively. Major resections were defined as resections of three or more

segments. Synchronous liver and bile-duct resections were performed in the presence of hilar cholangiocarcinoma. Radiofrequency ablation was used where small lesions were not accessible for surgical resection.

Major complications were defined as Grade III-V complications using the Dindo-Clavien classification where grade III complications are those requiring surgical, endoscopic or radiological intervention, grade IV includes life threatening complications including organ failure and grade V is death[296]. Post-hepatectomy liver failure (PHLF) was defined in accordance with the International Study Group of Liver Surgery (ISGLS)[187] as an increased prothrombin time (PT) and serum bilirubin concentration on or after postoperative day five. In patients with preoperatively increased PT or serum bilirubin concentration PHLF was defined as an increasing serum bilirubin concentration and PT on or after postoperative day 5, compared with the values of the previous day. Renal dysfunction was defined as an increase in serum creatinine of ≥1·5-fold from the preoperative baseline, according to RIFLE criteria[298].

Serum biochemistry tests and coagulation assays were performed pre-operatively, in the first 24 post-operative hours and then repeated according to clinical course. The peak measurement of bilirubin, prothrombin time (PT) and creatinine was recorded. Clotting factors were not administered between postoperative days (POD) 1-5. At histological examination the background liver parenchyma at least 1cm from the tumour edge was assessed for degree of steatosis using the Brunt classification (the proportion of hepatocytes containing fat droplets; 1: <33%, 2: 33–66%, 3: >66%)[299]. For analysis, the data was divided into <33% (mild or none) and ≥33% (moderate or severe).

The minimum post-operative follow-up was 90 days and mortality was recorded along with details of postoperative intervention and complications.

To determine potential associations between patient characteristics and steatosis, and between patient, operative and histological characteristics and major complications univariate logistic regression or chi-square test at the level of $P<0.25$[229] was performed, as appropriate. Significant variables in the univariate analysis were included in the multivariate logistic regression model and were considered to be significant if $P<0.05$. All analyses were carried out using the statistical package R 2.1.14[230].

6.4 Results

Of 504 patients treated in the study period surgery was undertaken for metastatic disease in 358 (71.0%), of whom 308 (61.1%) had colorectal liver metastases. Resections were performed for primary hepatic malignancy in 106 patients (21.0%) including hepatocellular carcinoma in 39 (7.7%) and cholangiocarcinoma in 31 (6.2%) patients. In 40 patients (7.9%) resection was performed for benign tumours. Major resection was undertaken in 299 patients (59.3%). In twenty-three patients, a synchronous bowel procedure was performed including 10 colonic resections, 11 small bowel procedures, one gastric resection and one Whipple's procedure. Fifty-six patients were diabetic (11.1%) of whom 15 were insulin-dependent (26.8%). The median BMI of patients undergoing resection was 26 kg/m^2 (range 16-54 kg/m^2). Elevated BMI ($\geq 25kg/m^2$) was noted in 332 patients (65.9%) and 123 patients (24.4%) were obese ($\geq 30kg/m^2$). Five patients had no BMI recorded and were excluded from

analysis. Preoperative liver-directed chemotherapy was used in 168 patients (33.3%). The most commonly used regime was oxaliplatin and capecitabine which was used in 118 patients (70.2%). Irinotecan was used in six patients (3.6%).

Histopathological examination revealed zero, mild, moderate and severe steatosis in 199 (39.5%), 179 (35.5%), 54 (10.7%) and seven (1.4%) patients respectively. Degree of steatosis was not recorded in 65 patients (12.9%). The distribution of BMI, diabetes and steatosis is shown in Figure 6.1.

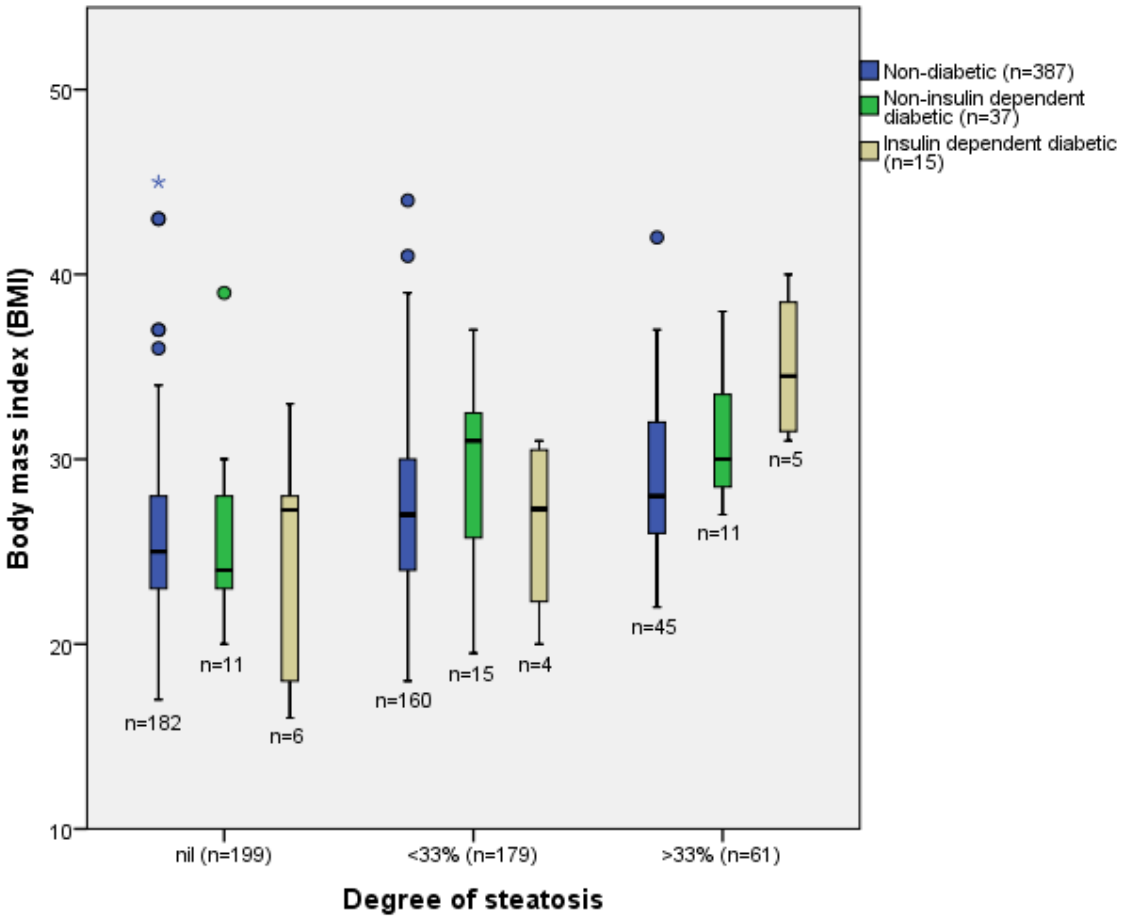


Figure 6.1 Box plot of body mass index (BMI), diabetic status and degree of hepatic steatosis in 439 patients undergoing liver resection.

Difference in distribution of BMI Nil vs <33% (P<0.001), <33 vs ≥33% (P=0.001)

The median BMI of patients with no steatosis (25kg/m^2, range 16-45) was lower than those with mild steatosis (27kg/m^2, range 18-44) (P<0.001), which was lower than patients with moderate/severe steatosis (29kg/m^2, range 22-42) (P=0.001). The median BMI of diabetic patients was 29kg/m^2 (16-40) compared to 26kg/m^2 (17-54) in non-diabetic patients (P=0.002). There was no difference in the median BMI of patients with insulin-dependent diabetes (IDDM) (29kg/m^2, range 16-40) and those with non-insulin dependent diabetes (NIDDM) (29kg/m^2, range 20-39) (P=0.816). The rate of mild steatosis among diabetics was 16/52 (30.8%) compared to 45/387 (11.6%) in non-diabetics (P=0.001), but there was no significant difference in the rates of mild steatosis in patients with NIDDM (11/37) and those with IDDM (5/15). The rate of moderate/severe steatosis was 6/135 (4.4%) in normal weight, non-diabetic patients, 39/249 (15.6%) in overweight non-diabetics (P=0.001), 0/12 in normal weight diabetics and 15/39 (38.5%) in overweight diabetics (P<0.001).

Elevated pre-operative transaminase levels were noted in 18 of 60 patients (30%) with moderate/severe steatosis and 61 of 369 patients (16.5%) with steatosis <33% (P=0.019). The sensitivity and specificity of elevated transaminases for predicting the presence of moderate or severe steatosis were 30% and 83% respectively.

Multivariate analysis revealed that elevated BMI ≥25kg/m^2 (P=0.001) and the presence of diabetes (P=0.018) were significantly associated with moderate/severe hepatic steatosis (Table 6.1).

N=439		Steatosis <33% (n=378)		Steatosis ≥33% (n=61)		Univariate	Multivariate		
		Median (range)	Count (%)	Median (range)	Count (%)	P-value	Comparison	Odds ratio (95% CI)	P-value
Age		65 (21-90)		65 (41-87)		0.622			
Gender	Female		168 (44.4)		24 (39.3)	0.544			
	Male		210 (55.6)		37 (60.7)				
Liver directed chemotherapy	Yes		132 (34.9)		20 (32.8)	1.000			
	No		246 (65.1)		41 (67.2)				
Pre-existing chronic liver disease	Yes		6 (1.6)		3 (4.9)	0.228*			0.869
	No		372 (98.4)		58 (95.1)				
Preoperative jaundice (≥50micromol/L)	Yes		5 (1.3)		0	0.800			
	No		373 (98.7)		61 (100)				
Hypoalbuminaemia (<35g/L)	Yes		15 (4.0)		1 (1.6)	0.602			
	No		360 (95.2)		59 (96.7)				
	Not recorded		3 (0.8)		1 (1.6)				
Raised preoperative alkaline phosphatase	Yes		92 (24.3)		5 (8.2)	0.008*		0.15 (0.05-0.46)	0.001**
	No		283 (74.9)		55 (90.2)				
	Not recorded		3 (0.8)		1 (1.6)				
Raised preoperative transaminase	Yes		61 (16.1)		18 (29.5)	0.021*		3.82 (1.85-7.89)	<0.001**
	No		308 (81.5)		42 (68.9)				
	Not recorded		9 (2.4)		1 (1.6)				
Diabetic status	Non-diabetic		342 (90.5)		45 (73.8)	0.001*			
	Non-insulin dependent		26 (6.9)		11 (18.0)		Diabetic vs non-diabetic	2.69 (1.18-6.13)	0.018**
	Insulin dependent		10 (2.6)		5 (8.2)		Insulin dependent vs non-insulin	4.31 (1.09-16.98)	0.037**
Body mass index (kg/m^2)	<25		141 (37.3)		6 (10)	<0.001*	<25 vs ≥25	2.97 (1.59-5.57)	0.001**
	25-29.9		153 (40.5)		27 (45.0)				
	≥30		81 (21.4)		27 (45.0)		25-29.9 vs ≥30		0.144
	Not recorded		3 (0.8)		1 (1.6)				

Table 6.1 Analysis of factors associated with hepatic steatosis (≥33%) in 439 patients undergoing liver resection.

***Significant at the level of 0.25 for univariate analysis and included in multivariate analysis **Significant at the level of 0.05 for multivariate analysis**

Body Mass Index ≥25kg/m^2 increased the risk by a factor of 2.97 and diabetes increased the risk by a factor of 2.69. Among diabetic patients, insulin-dependence increased the risk of moderate/severe steatosis by a factor of 4.31 (P=0.037). However, BMI ≥30kg/m did not increase the risk of moderate/severe steatosis compared to BMI of 25-29.9 (P=0.144). Raised preoperative transaminase levels also increased the risk of moderate/severe steatosis by a factor of 3.82 (P<0.001) and raised preoperative alkaline phosphatase concentrations decreased the risk by a factor of 0.15 (P=0.001). Hepatic steatosis was not associated with liver-directed chemotherapy or other biochemical markers of liver dysfunction (pre-operative hypoalbuminemia and hyperbilirubinaemia).

During the study period 94 patients developed a major postoperative complication. Twenty-three patients died within 90 days of surgery (4.6%) and 71 patients who survived beyond 90 days suffered a major complication (14.1%). The most common cause of mortality was liver failure (nine patients).

Of patients who developed Grade IV complications 34/64 (53.1%) developed PHLF and 31/64 developed renal failure (48.4%). Of the 34 patients who developed PHLF 29 had undergone major liver resection. Twenty-three patients developed bile leaks, and seven required relaparotomy/relaparoscopy. Multivariate analysis revealed that older age, male gender, hypoalbuminaemia, synchronous bowel procedures, number of segments resected, and blood transfusion were independent risk factors for major postoperative complications (Table 6.2).

N=504			No complication (n=410)	Major complication (n=94)	Univariate	Multivariate	
					P-value	Odds ratio (95% CI)	P-value
Median age (range)			64 (21-90)	67 (32-88)	0.015*	1.03 (0.99-1.07)	0.004**
Gender (%)	Male		211 (51.5)	67 (71.3)	0.001*	2.36 (1.34-4.17)	0.028**
	Female		199 (48.5)	27 (28.7)			
Pathology (%)	Benign		34 (8.3)	6 (6.4)			
	Primary		83 (20.2)	23 (24.5)	0.622		
	Secondary		293 (71.5)	65 (69.1)	0.308		
Liver directed chemotherapy (%)			130 (31.7)	33 (35.1)	0.608		
Pre-existing chronic liver disease (%)			10 (2.4)	1 (1.1)	0.666		
Preoperative jaundice (≥50micromol/L) (%)			6 (1.5)	3 (3.2)	0.266		
Hypoalbuminaemia (<35g/L) (%)			9 (2.2)	8 (8.5)	0.004*	2.97 (1.01-8.74)	0.047**
Raised preoperative alkaline phosphatase (%)			95 (23.2)	24 (25.5)	0.721		
Raised preoperative transaminase (%)			74 (18.0)	21 (22.3)	0.320		
Preoperative glomerular filtration rate (%)	≤90ml/min		274 (66.8)	63 (67.0)	0.892		
Median preoperative haemoglobin (g/dL) (range)			13 (9-17)	13 (9-16)	0.025*		0.439
Median preoperative white cell count (/L) (range)			7 (3-17)	7 (3-25)	0.422		
Diabetic status (%)	Non-diabetic		370 (90.2)	78 (83.0)	0.014*		0.912
	Non-insulin dependent (vs non-diabetic)		32 (7.8)	9 (9.6)			
	Insulin dependent diabetes (vs non-insulin dependent and non-diabetics)		8 (2.0)	7 (7.4)		3.86 (1.17-12.75)	0.028**
Body mass index (kg/m^2) (%)	<25		139 (33.9)	28 (29.8)	0.697		
	25-30		167 (40.7)	42 (44.7)			
	>30		99 (24.1)	24 (25.5)			
American Association of Anesthesiologists (ASA) grade (%)	1 vs 2	1	46 (11.2)	6 (6.4)	0.198*		0.611
		2	266 (64.9)	58 (61.7)			
	2 vs 3 and 4	3	95 (23.2)	30 (31.9)			0.783
		4	2 (0.5)	0			
Median P-POSSUM physiologic score (range)			16 (12-32)	18 (12-30)	0.003*		0.764
Operative approach (%)	Laparoscopic		46 (11.2)	4 (4.3)	0.065*		0.812
	Open		364 (88.8)	90 (95.7)			

Table 6.2 Analysis of factors associated with major complications following liver resection in 504 patients.

Table 6.2 continued.

N=504		No complication (n=410)	Major complication (n=94)	Univariate	Multivariate	
				P-value	Odds ratio (95% CI)	P-value
Radiofrequency ablation included (%)		18 (4.4)	5 (5.3)	0.698		
Wedge resection included (%)		181 (44.1)	22 (23.4)	<0.001*		0.353
Bile duct reconstruction (%)		34 (8.3)	12 (12.8)	0.246*		0.585
Synchronous bowel procedure (%)		13 (3.2)	10 (10.6)	0.003*	5.99 (2.25-15.96)	<0.001**
Median number of segments resected (range)		3 (1-6)	4 (1-6)	<0.001	1.51 (1.26-1.80)	<0.001**
Repeat operation (%)		31 (7.6)	6 (6.4)	0.861		
Intraoperative blood loss (%)	<500ml	218 (53.2)	29 (30.9)	<0.001		0.463
	≥500ml	188 (45.9)	65 (69.1)			
Blood transfusion required (%)		65 (15.9)	41 (43.6)	<0.001	2.48 (1.44-4.30)	0.001**
Steatosis (%)	<33%	308 (75.1)	70 (74.5)	1.000		
	≥33%	50 (12.2)	11 (11.7)			

*** Significant at the level of 0.25 for univariate analysis and included in multivariate analysis**
****Significant at the level of 0.05 for multivariate analysis**

There was no association between NIDDM, BMI or degree of hepatic steatosis and major postoperative complications. IDDM more than trebled the risk of major complication compared to non-diabetics and those with NIDDM. The complications in these groups are shown in Table 6.3.

The greatest risk however occurred when liver resection was undertaken in conjunction with a synchronous bowel procedure, which increased the risk of major complication almost six times that of a liver-only resection. Ten of 23 patients developed major postoperative complications, six of whom had colonic resections (three right sided and three left sided), three had small bowel procedures and one a gastric resection.

Of the 299 patients who underwent major resection there was no significant difference in the proportion of patients with steatosis ≥33% between patients who did (10/64, 15.6%) or did not (23/201, 11.4%) develop major complications (P=0.388). Similarly, there was no significant difference in the proportion of patients with steatosis ≥33%between patients who did (4/22, 15.6%) or did not (29/243, 11.9%) develop PHLF (P=0.495).

N=504		All patients (n=504)	Non-diabetic (n=448)	Non-insulin dependent diabetes (n=41)	Insulin dependent diabetes (n=15)	P-value Non diabetic vs non-insulin dependent diabetic	P-value Non-diabetic vs insulin dependent diabetic
		Count (%)	Count (%)	Count (%)	Count (%)		
Any major complication		94 (18.7)	78 (17.4)	9 (21.9)	7 (46.6)	0.521	0.010
90-day mortality (Grade V)	Liver failure	9 (1.8)	5 (1.1)	3	1	0.023	0.180
	Sepsis	4 (0.8)	3 (0.7)	1	0	0.296	1.000
	Malignancy	4 (0.8)	3 (0.7)	0	1	1.000	0.124
	Pulmonary embolus	1 (0.2)	1 (0.2)	0	0	1.000	1.000
	Anastomotic leak	1 (0.2)	1 (0.2)	0	0	1.000	1.000
	Peptic ulcer	1 (0.2)	1 (0.2)	0	0	1.000	1.000
	Strangulated hernia	1 (0.2)	1 (0.2)	0	0	1.000	1.000
	Peritonitis	1 (0.2)	1 (0.2)	0	0	1.000	1.000
	Heart failure	1 (0.2)	1 (0.2)	0	0	1.000	1.000
	Total	23 (4.6)	17 (3.8)	4	2	0.089	0.122
Grade IV complications	Post hepatectomy liver failure (PHLF)	34 (6.7)	30 (6.7)	4	0	0.515	0.613
	Renal dysfunction	31 (6.2)	24 (5.4)	4	3	0.280	0.050
	Respiratory failure requiring Intensive Care	2 (0.4)	2 (0.4)	0	0	1.000	1.000
	Total	67 (13.3)	56 (12.5)	8	3	0.224	0.421

Table 6.3 Postoperative complications, 90-day mortality and diabetic status in 504 patients undergoing liver resection.

N=504			All patients (n=504)	Non-diabetic (n=448)	Non-insulin dependent diabetes (n=41)	Insulin dependent diabetes (n=15)	P-value Non diabetic vs non-insulin dependent diabetic	P-value Non-diabetic vs insulin dependent diabetic
			Count (%)	Count (%)	Count (%)	Count (%)		
Grade III complications	Bile leak	Drain	12 (2.4)	11 (2.5)	0	1	0.611	0.330
		ERCP	11 (2.2)	10 (2.2)	1	0	1.000	1.000
	Re-laparotomy/ laparoscopy	Washout	3 (0.6)	1 (0.2)	1	1	0.161	0.064
		Adhesiolysis	2 (0.4)	2 (0.4)	0	0	1.000	1.000
		Defunction for anastomotic leak	1 (0.2)	0	1	0	0.084	1.000
		Small bowel leak	1 (0.2)	1 (0.2)	0	0	1.000	1.000
	Drainage	Liver abscess	1 (0.2)	1 (0.2)	0	0	1.000	1.000
		Pleural effusion	1 (0.2)	0	0	1	1.000	0.032
		Pneumothorax	1 (0.2)	1 (0.2)	0	0	1.000	1.000
		Subphrenic collection	2 (0.4)	2 (0.4)	0	0	1.000	1.000
	Total		35 (6.9)	29 (6.5)	3	3	0.743	0.077

Table 6.3 continued.

Patients may have had more than one complication.

6.5 Discussion

The principal finding of this study is that although diabetes mellitus and higher BMI are risk factors for steatosis in patients undergoing liver resection, the majority of cases of steatosis occur in non-diabetic patient with mildly elevated BMI (25-30). Secondly, steatosis and elevated BMI are not associated with major complications after liver resection, and diabetes is a risk factor for these complications only if patients are insulin dependent. Other predictors of major complications are older age, male gender, preoperative hypoalbuminaemia, synchronous bowel procedures, number of segments resected and requirement for blood transfusion.

The 90-day mortality (4.6%) and morbidity rate (14.7%) rate are similar to published series[136,137,270], although other series have included minor (Grade I and II) complications[161,300,301]. Composite outcomes similar to the one used in this study have been used previously in studies evaluating outcomes following gastrointestinal surgery[302,303]. The present study confirms the association between hepatic steatosis and BMI[304]. Whilst the rate of moderate/severe steatosis was greatest in overweight diabetic patients (38.5%), it also occurred in patients of normal weight without diabetes (4.4%). This suggests that other risk factors may be involved in the aetiology of the disease. Undernutrition [291], impaired glucose tolerance[305] and genetic factors[306] have also been implicated in the development of NAFLD. Alcohol consumption is an unlikely cause of steatosis in this series as all patients are asked to abstain from alcohol consumption prior to surgery, although compliance with this instruction has not been assessed.

Elevated transaminase levels are associated with hepatic steatosis, but the sensitivity of abnormal transaminases in detecting moderate or severe NAFLD is poor, as 70% of these patients had normal transaminase levels. This is in keeping with other studies[307]. Interestingly, raised preoperative alkaline phosphatase concentration was associated with decreased incidence of steatosis. Elevated alkaline phosphatase may be found in cases of biliary obstruction and of the 119 patients with this finding 16.8% had cholangiocarcinomas compared to only 2.9% of the 380 patients with normal alkaline phosphatase. This group is more likely to be systemically unwell as a consequence of biliary obstruction and to have suffered a period of anorexia and weight loss, which may affect the degree of hepatic steatosis.

Pre-operative chemotherapy was not shown to be associated with steatosis. Studies have shown an association between steatohepatitis and irinotecan therapy[270], which was rarely used in this series. In addition, the policy in this unit is to use only four cycles of chemotherapy and to allow a period of recovery before undertaking liver resection, to allow resolution of hepatotoxicity.

Previous studies have shown that steatosis increases the risk of PHLF [111,283]. The rate of PHLF in this series was low (6.7%), and occurred in 6.6% patients with moderate/severe steatosis and 6.1% of the patients with none/mild steatosis. The majority of cases of PHLF followed major liver resection (29/34). It is possible that there is an independent association between steatosis and PHLF, which is not revealed in this study which uses a composite outcome including other complications in the multivariate analysis. Steatosis may be a risk factor for liver failure in patients undergoing extended hepatectomy, although not in major hepatectomy in this series, where the risk of this

complication is greatest. Previous studies have recommended liver biopsy to investigate the presence of steatosis prior to resection[308,309]. The current study suggests that the risk of this investigation is not justified due to the lack of effect of steatosis on outcome.

The rate of bile leak requiring intervention (4.6%) was not affected by the degree of hepatic steatosis suggesting that hepatic steatosis does not make parenchymal division more difficult to perform.

Elevated BMI was not associated with major complications in this series, although it may be associated with more minor complications such as wound infection which has not been explored in this study.

Diabetes was an independent risk factor for complications after liver surgery which confirms the findings of previous studies[60,163,164,282], although identification of insulin-dependence as the major risk factor is a novel finding. Whilst there was no significant difference in the risk of major complications between non-diabetic patients and those with non-insulin dependent diabetes, the risk of complications was more than trebled in those with insulin-dependent diabetes. This finding reflects the multi-system nature of diabetic end-organ damage. Diabetic nephropathy is a major cause of renal dysfunction[310] and was the most common complication in patients with IDDM. Renal dysfunction was also twice as common amongst patients with IDDM compared to those with NIDDM.

Older age, male gender, preoperative hypoalbuminaemia, number of liver segments resected and requirement for blood transfusion have all been previously identified as risk factors for postoperative complications[136]. The

finding that performing a synchronous bowel procedures is associated with worse outcome is similar to that of a previous study which found that the risk of a major complication was 20.4% after a synchronous colonic resection compared to 14.9% after a liver only resection[311]. Although a recent systematic review suggested no difference in terms of overall morbidity or mortality between synchronous or staged resections[312] the results of the present study reveal the risk of developing a major complication after a synchronous bowel procedure was almost six times that of a liver-only resection. It should also be noted that the synchronous procedures included a gastric resection and a Whipple's procedure which may pose different risks to colonic resections. Most of the increased risk in this context relates to leaks from enteric anastomoses.

6.6 Conclusions

The results of this study allow clinicians to advise patients regarding the risks of liver resection and to place them in context. In particular, liver surgery in the presence of steatosis, elevated BMI and NIDDM does not lead to greatly increased operative risk. While insulin dependence is a significant risk factor for complications after liver surgery the major risk factors in this series related to technical details of the operation, particularly the performance of simultaneous bowel procedures. Clinicians should counsel patients preoperatively regarding their individual risks associated with liver resection so that they can make informed decisions regarding their care

Chapter 7: Serum arterial lactate concentration is a useful predictor of mortality and organ dysfunction following liver resection

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7.1 Abstract

Introduction

The aim of this study was to determine if the post-operative serum arterial lactate concentration is associated with mortality, length of hospital stay or complications following hepatic resection.

Methods

Serum lactate concentration was recorded at the end of liver resection in a consecutive series of 488 patients over a seven-year period. Liver function, coagulation and electrolyte tests were performed post-operatively. Renal dysfunction was defined as a creatinine rise of >1.5x the preoperative value.

Results

The median lactate was 2.8mmol/L (0.6-16mmol/L) and was elevated (≥2mmol/L) in 72% of patients. The lactate concentration was associated with peak post-operative bilirubin, prothrombin time, renal dysfunction, length of

hospital stay and 90-day mortality (P<0.001). The 90-day mortality in patients with a post-operative lactate ≥6mmol/L was 28% compared to 0.7% in those with lactate ≤2mmol/L. Pre-operative diabetes, number of segments resected, the surgeon's assessment of liver parenchyma, blood loss and transfusion were independently associated with lactate concentration.

Conclusions

Initial post-operative lactate concentration is a useful predictor of outcome following hepatic resection. Patients with normal post-operative lactate are unlikely to suffer significant hepatic or renal dysfunction and may not require intensive monitoring or critical care.

7.2 Background

Despite advances in both operative technique and peri-operative care liver resection is associated with postoperative mortality rates of 0-22% (median 3.7%)[136] and morbidity rates of 12.5%- 66% including liver dysfunction[186,313], renal dysfunction[140] and bile leak[195,314]. Factors associated with peri-operative complications and death include patient age[146,148] and gender[143,153] hospital annual number of liver resections undertaken[143,145], pathologic origin of liver tumour[143,145], preoperative liver and renal dysfunction[148,153], diabetes[163,164], chronic liver disease[143,146], and the peripheral neutrophil to lymphocyte ratio (NLR)[168]. Operative factors associated with outcome include blood loss[148,153] and transfusion[63,167], extent of liver resection[63,147], duration of surgery[155], simultaneous extrahepatic procedures[63,172], and the use of the Pringle manoeuvre[149,167].

Therefore, many factors affect outcome after liver surgery which have not been incorporated into a single scoring system. The American Society of Anaesthesiologists (ASA) grade and Portsmouth Physiologic and Operative Severity Score for the enUmeration of Mortality and morbidity (P-POSSUM) scores are used in the risk prediction of many types of surgery[297,315] including liver surgery[316]. However, these scores may not be applicable to the unique stresses of liver resection. One of the main reported causes of mortality following liver resection is post-hepatectomy liver failure (PHLF)[138]. The “50-50 criteria” of serum bilirubin of >50µmol/L and prothrombin index (laboratory's calculated mean normal PT divided by patient's observed PT) of <50% measured on the fifth postoperative day has been shown to be associated with death due to PHLF[186]. More recently PHLF has been defined by the International Study Group of Liver Surgery (ISGLS) as an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinaemia on or after postoperative day five[187]. The ability of this newer definition of PHLF, using lower measures of dysfunction, to predict mortality is assessed in the next chapter but a prediction system based on criteria before postoperative day five may be clinically more useful in guiding therapy. Furthermore, failure of multiple organ systems may contribute to death following liver resection and there is a need for a global peri-operative measure to predict the risk of developing significant post-operative morbidity and death.

Lactic acid is a by-product of anaerobic metabolism which is subsequently metabolised in the liver during gluconeogenesis[114]. Hyperlactataemia has been shown to be associated with increased mortality and morbidity in a critical care setting[118,317], in patients with liver failure[119], sepsis[120] and following trauma[318].

Similar relationships have been shown in the postoperative setting following pancreatic resection[319] and other major abdominal surgery[121], cardiac surgery[320] and after hepatic transplantation[321].

The primary aim of this study was to determine if the first post-operative arterial lactate concentration ('initial lactate') is associated with adverse outcomes following liver resection including 90-day mortality, length of hospital stay (LOS), and renal and hepatic dysfunction. The secondary aim was to determine which pre- and intra-operative risk factors are associated with initial lactate concentration following liver resection.

7.3 Methods

This study was a retrospective analysis of a prospectively maintained database of all patients undergoing liver resection since July 2005. Routine patient characteristics, laboratory data and intra-operative details were retrieved. Pre-operative liver-directed chemotherapy was administered to selected patients following discussion at a regional multidisciplinary team meeting. A period of recovery of at least six weeks was allowed following cessation of chemotherapy before undertaking surgery. The POSSUM scoring system was used to calculate the physiological score[297]. Prior to resection the operating surgeon makes a visual assessment of the condition of the liver parenchyma and records this as normal or abnormal. Liver resections were performed using standard techniques with a *Cavitron Ultrasonic Surgical Aspirator*® *(*CUSA) dissector. Hepatic inflow occlusion was used in a minority of cases where there was excessive blood loss. Anaesthetic techniques include the routine use of

invasive arterial blood pressure monitoring, central venous pressure monitoring (using a target CVP of <5cm H_20) and epidural anaesthesia. Liver resections were defined according to the Brisbane classification[17] and the number of removed segments recorded. Intravenous fluid replacement was minimised during the resection phase to decrease venous pressure. After removal of the surgical specimen a pause in surgical activity is routinely planned to allow haemostasis and intra-venous volume replacement with 0.9% Saline or Hartmann's solution at the anaesthetist's discretion. Patients are usually returned to the High Dependency Unit (HDU) after surgery with full invasive monitoring, except for minor resections in fit patients who are returned to the general ward.

The serum lactate was recorded from an arterial blood sample taken immediately prior to abdominal closure or immediately on arrival in the HDU. The arterial lactate in the normal population is below 1.6mmol/L whereas in a critical care setting <2mmol/L is more commonly accepted in acutely stressed patients[322].

Serum biochemistry tests and coagulation assays were performed on all patients in the first 24 hours post-operatively and the tests repeated according to clinical course. The peak measurement of bilirubin and prothrombin time (PT) were recorded and used for analysis. A PT index of <50% corresponds to a PT>24s. Similarly peak postoperative creatinine levels were obtained and renal dysfunction was defined according to RIFLE criteria[298]. Renal dysfunction in categorical analyses was defined as any increase in serum creatinine of ≥1·5-fold from the preoperative baseline. The length of hospital stay was measured

from the day of surgery to day of discharge and was expressed as a natural logarithm. Ninety-day mortality was recorded.

The association between initial serum lactate concentration and continuous outcomes was investigated using a multiple linear regression model as well as Spearman's rank correlation. To overcome increasing variance with the mean a natural log transformation was used. Binary variables were investigated using univariate regression. Potential associations between initial lactate concentration and pre- and intraoperative factors were tested using univariate regression or chi-square test at the level of $P<0.25$[229], as appropriate. Significant variables in the univariate analysis were included in the multivariate regression model and were considered to be significant if $P<0.05$. All analyses were carried out using the statistical package R 2.1.14[230].

Confirmation was obtained from the regional health research authority that under the harmonized Guidance Approval for Research Ethics Committees (REC), REC review was not required because patient data were collected during their normal hospital care and was anonymised for research purposes. No patient consent was required for this study.

7.4 Results

In the study period 501 patients underwent liver resection for whom an initial lactate measurement was available in 488. The indications for surgery, pre-operative and operative details are shown in Table 7.1. Results of blood tests are shown in Table 7.2 and the main post-operative outcome measures are summarised in Table 7.3. The median number of biochemistry tests performed

per patient in the first five post-operative days was 4 (0-6) and coagulation assays was 3 (0-6). It was not necessary to administer clotting factors to any surviving patients between postoperative days 1-5. Peak abnormalities in PT and bilirubin usually occurred early in the post-operative course and tended to improve over five days (Table 8.2). Post-operatively 118 patients (24.1%) had a serum bilirubin ≥50μmol/L. Minor abnormalities in PT were commonly noted though only 15 patients (3.1%) developed a PT >24s. Although a small number of patients remained jaundiced at the time of discharge, only one patient fulfilled the “50-50 criteria” at day five. The median length of hospital stay was seven days (range 2-78) with 90% of patients having a LOS between two and 15 days. Twelve patients (2.5%) died within 30 days of surgery and 23 died within 90 days of surgery (4.7%). The most common cause of death was liver failure which occurred in 11 of 23 patients. Four patients died from on-going malignancy (of whom three had undergone non-curative resections) and two patients died from sepsis without evidence of liver failure. The remaining deaths were attributed to pulmonary embolus, heart failure, anastomotic leak following colonic resection, bleeding peptic ulcer, strangulated hernia and peritonitis.

N=488			Median (Range)	Count (%)
Age (years)			65 (21-90)	
Gender	Female			216 (44.3)
	Male			272 (55.7)
Pathology of resected specimen	Benign			40 (8.2)
	Primary	Hepatocellular carcinoma		30 (6.1)
		Cholangiocarcinoma		36 (7.4)
		Other		35 (7.2)
	Secondary	Colorectal metastases		291 (59.6)
		Other		56 (11.5)
Preoperative liver directed chemotherapy	Yes			173 (35.5)
	No			315 (64.5)
Body Mass Index			26 (16-54)	
POSSUM Physiologic score			16 (12-32)	
ASA Grade	1			49 (10.1)
	2			315 (64.7)
	3			121 (24.8)
	4			2 (0.4)
Preoperative diabetes	Yes			55 (11.3)
	No			433 (88.7)
Preoperative bilirubin (µmol/L)			9 (2-162)	
Preoperative alkaline phosphatase (U/L)			95 (34-1190)	
Preoperative albumin (g/L)			44 (10-53)	
Preoperative creatinine (µmol/L)			78 (40-430)	
Preoperative Glomerular Filtration Rate (ml/min)	≤90			158 (33.2)
	>90			318 (66.8)
Neutrophil to Lymphocyte Ratio (NLR)			2.47 (0.3-17.3)	
Operation number	1st			453 (92.8)
	2nd			30 (6.1)
	3rd			5 (1.0)
Surgeons assessment of liver parenchyma	Normal			314 (65.3)
	Abnormal			167 (34.7)
Surgical approach	Open			440 (90.2)
	Laparoscopic			48 (9.8)
Radiofrequency ablation (RFA) included	Yes			22 (4.5)
	No			466 (95.5)
Operation	Right hemihepatectomy			142 (29.1)
	Extended right hemihepatectomy			65 (13.3)
	Left hemihepatectomy			55 (11.3)
	Extended left hemihepatectomy			24 (4.9)
	Left lateral sectorectomy			45 (9.2)
	Wedge resection only			127 (26.0)
	Other			30 (6.1)
Wedge resection included	Yes			182 (37.3)
	No			306 (62.7)

Table 7.1 Preoperative and intraoperative characteristics of 488 patients undergoing liver resection

Table 7.1 continued.

N=488		**Median (Range)**	**Count (%)**
Bile duct reconstruction included	Yes		43 (8.8)
	No		445 (91.2)
Synchronous bowel procedure	Yes		22 (4.5)
	No		466 (95.5)
Curative intent	Yes		442 (90.6)
	No		46 (9.4)
Number of segments resected		4 (1-6)	
Estimated blood loss	<100ml		2 (0.4)
	101-500ml		240 (49.7)
	501-1000ml		167 (34.6)
	>1000ml		74 (15.3)
Units of red cells transfused		0 (0-26)	

N=488		POD 0	POD 1	POD 2	POD 3	POD 4	POD 5
Bilirubin	Tested (%)	393 (81)	385 (79)	324 (66)	255 (52)	213 (44)	200 (41)
	Median (range)	21 (5-170)	27 (6-211)	21 (4-195)	19 (3-167)	18 (4-179)	19 (1-186)
PT	Tested (%)	387 (79)	317 (65)	233 (48)	170 (35)	135 (28)	107 (22)
	Median (range)	16.3 (12.2-32.4)	18.0 (12-200)	18.0 (12.6-39.4)	16.1 (11.2-37.2)	15.3 (11.6-30.6)	15.4 (12.0-26.4)
Creatinine	Tested (%)	425 (87)	458 (94)	374 (77)	288 (59)	241 (49)	226 (46)
	Median (range)	70 (30-319)	70.5 (29-377)	64.5 (26-686)	60.5 (28-518)	59 (25-611)	60 (26-292)

Table 7.2 Postoperative blood tests for 488 patients undergoing liver resection

N=488		Median (range)	Count (%)
Peak bilirubin (μmol/L)		29 (4-445)	
Peak prothrombin time (s)		17.6 (12.4-200)	
Length of stay (days)		7 (2-78)	
Renal dysfunction	None		450 (92.2)
	Risk (>1.5x pre-operative creatinine)		17 (3.5)
	Injury (>2x pre-operative creatinine)		12 (2.5)
	Failure (>3x pre-operative creatinine)		5 (1.0)
90-day mortality			23 (4.7)

Table 7.3 Postoperative outcomes for 488 patients undergoing liver resection

The median initial lactate concentration was 2.8mmol/L (inter-quartile range = 1.9-3.9) and 350 patients (72%) had an elevated serum lactate concentration (≥2mmol/L) (Figure 7.1).

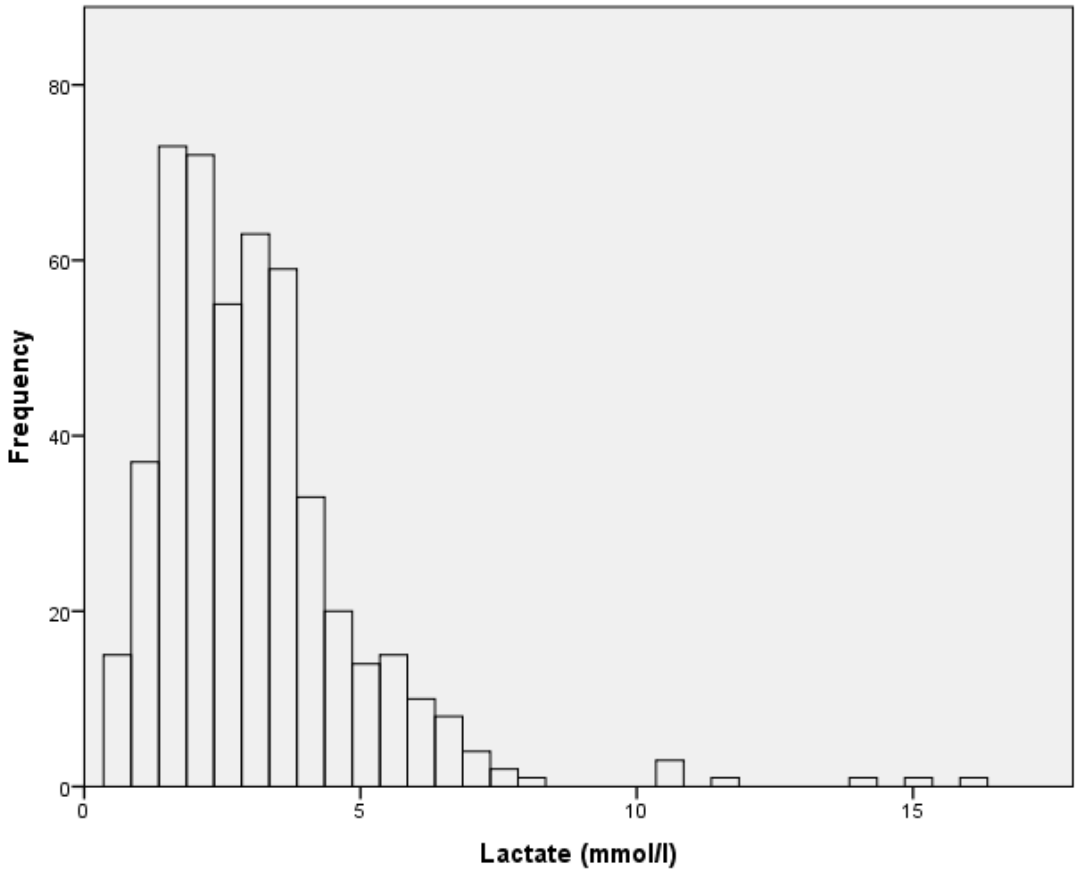


Figure 7.1 Distribution of arterial lactate concentration in 488 patients at the end of liver resection

There was no difference in the lactate concentration taken prior to abdominal closure (n=380, median 2.8mmol/L, range 0.6-16.0) or immediately on arrival in the HDU (n=108, median 2.8mmol/L, range 0.6-14.0). The initial lactate concentration was noted to be associated with all recorded outcome measures (Table 7.4).

N=488	Coefficient ±SD	P-value
Peak bilirubin	0.146 ± 0.017	<0.001*
Peak prothrombin time	0.055 ± 0.002	<0.001*
Length of Stay	0.046 ± 0.006	<0.001*
Renal dysfunction	0.324 ± 0.072	<0.001*
90-day mortality	0.373 ± 0.079	<0.001*

Table 7.4 Univariate analysis of the association between lactate and postoperative outcomes for 488 patients undergoing liver resection.

***Significant at level of P<0.05**

Although major abnormalities of serum bilirubin and PT were rare in our series there was a weak correlation with initial lactate for both bilirubin (coefficient 0.41, P<0.001) and PT (coefficient 0.37, P<0.001) which was stronger for bilirubin. Similarly, there was a weak correlation with length of hospital stay (coefficient 0.28, P<0.001). Of note the values for length of hospital stay includes only survivors, and therefore excludes some patients who are likely to have high post-operative lactate levels. Renal dysfunction after liver resection was rare in this series (7.0%) but there was a correlation with lactate concentration (Table 7.4). Three of 137 patients (2.2%) with an initial lactate concentration less than 2mmol/L who had creatinine measured developed renal dysfunction (negative predictive value (NPV) = 0.98) compared to 8 of 29 (27.5%) patients with an initial lactate greater than 6mmol/L (positive predictive value (PPV) = 0.28) (P=<0.001) (Figure 7.2).

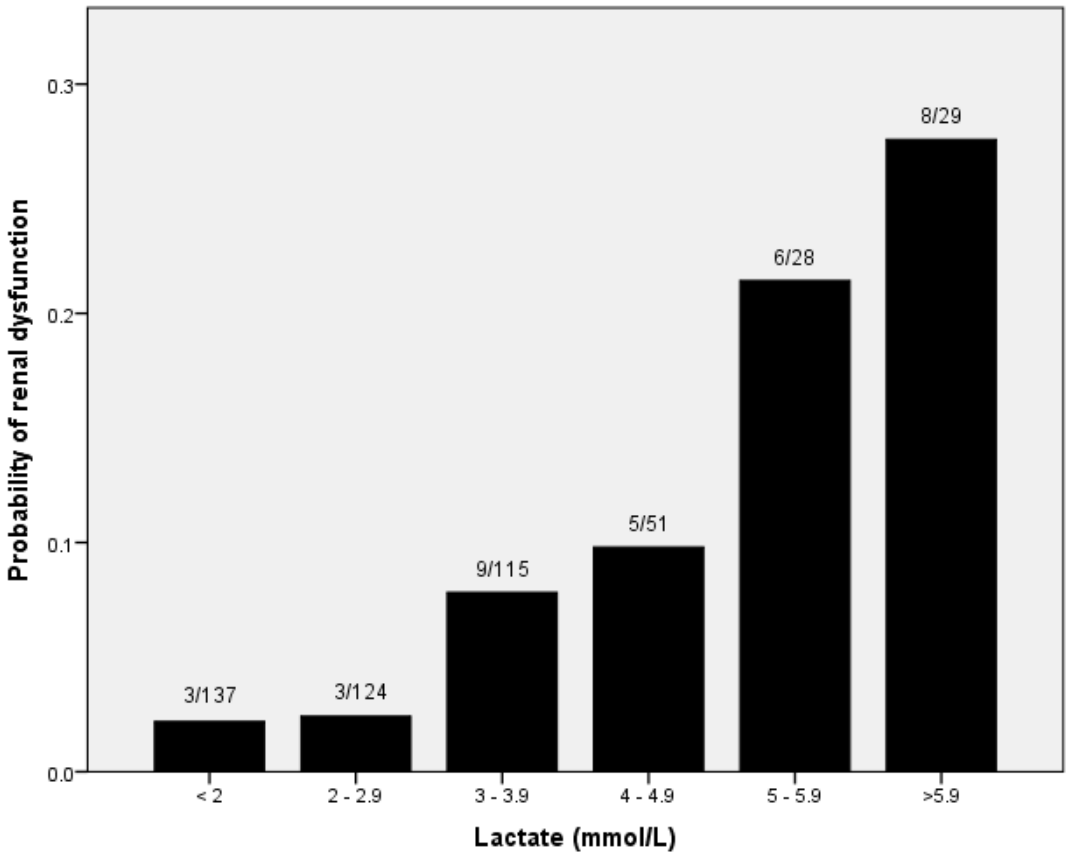


Figure 7.2 Probability of renal dysfunction after liver resection according to lactate concentration in 484 patients

In 322 patients with a lactate concentration ≥2 and <6mmol/L 23 developed renal dysfunction (7.1%).

Similarly, there was a correlation between mortality in the 90-day period following liver resection and initial lactate concentration (Table 7.4). One of 138 patients (0.7%) with an initial lactate concentration <2mmol/L died within this period, due to an anastomotic leak following colonic resection (NPV=0.99), compared to eight of 29 patients with initial lactate ≥6mmol/L (PPV = 0.28) (P=<0.001) (Figure 7.3).

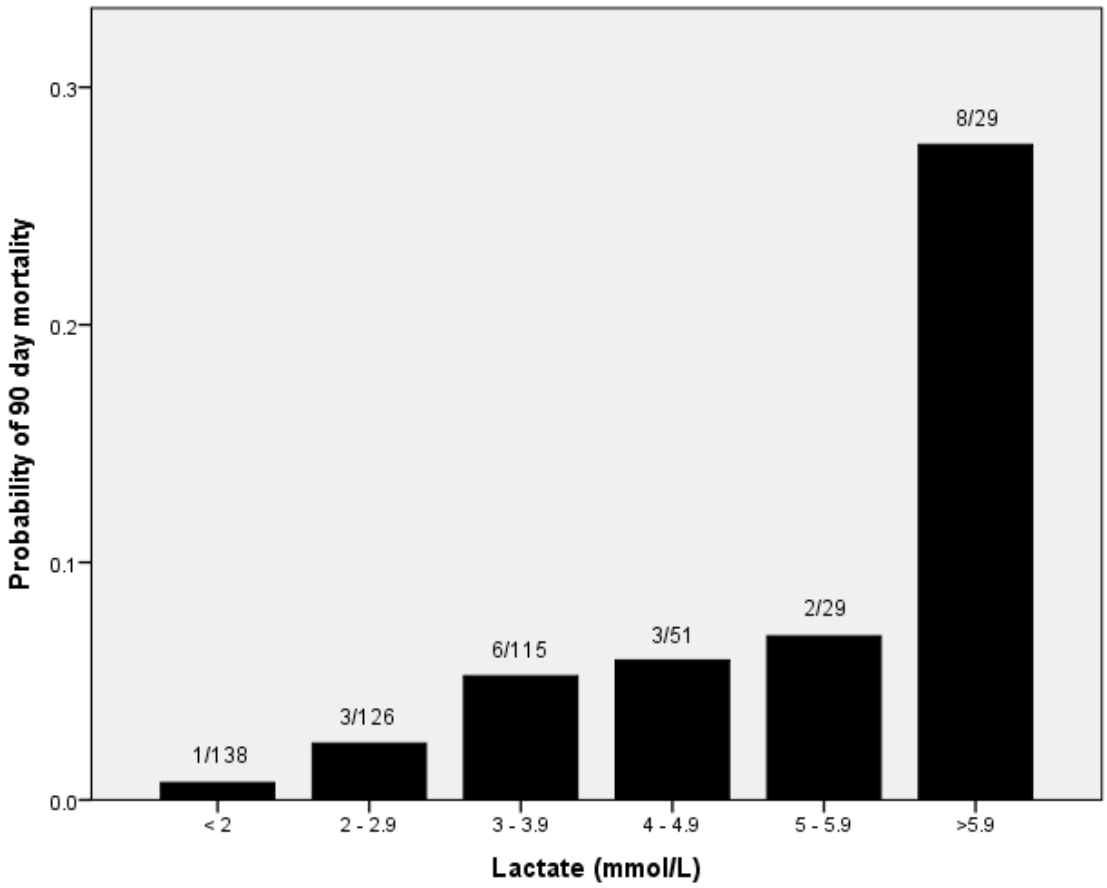


Figure 7.3 Probability of 90-day mortality after liver resection according to lactate concentration in 488 patients

The deaths in patients with lactate ≥6mmol/L were due to liver failure in four patients, sepsis without liver failure in two patients, cardiac failure in one patient and on-going malignancy in the other. Of the remaining 322 patients with lactate concentration ≥2 and <6mmol/L there were 14 deaths within 90 days of surgery (4.3%).

Comparison of patients with initial lactate concentrations <2mmol/L and ≥6mmol/L revealed there were significantly more major resections performed (P<0.001) and more patients with preoperative diabetes (P<0.001) in patients with a lactate concentration ≥6mmol/L (Table 7.5).

Lactate	<2mmol/L (n=138)	≥6mmol/L (n=29)	P-Value
Major resection (%)	26 (18.8)	26 (89.7)	<0.001*
Preoperative chemotherapy (%)	38 (27.5)	5 (17.2)	0.351
Preoperative diabetes (%)	6 (4.3)	8 (27.6)	<0.001*
Postoperative renal dysfunction (%)	3 (2.2)	8 (27.6)	<0.001*
90-day mortality (%)	1 (0.7)	8 (27.6)	<0.001*

Table 7.5 Distribution of risk factors and outcomes in 138 patients with lactate <2mmol/L and 29 patients with lactate ≥6mmol/L undergoing liver resection

***Significant at level of P<0.05**

There was no significant difference in the use of preoperative chemotherapy between these two groups (P=0.351). The proportion of patients with both renal dysfunction and who died within 90 days was significantly higher in those with lactate concentrations ≥6mmol/L (P<0.001).

Regression analysis revealed that a preoperative diagnosis of diabetes mellitus, the number of liver segments resected, the operating surgeon's assessment of the health of the liver parenchyma, the operative blood loss and number of units of red cells transfused were all independently associated with initial lactate concentration at closure (Table 7.6). The only preoperative factor associated with the post-operative lactate concentration was the presence of diabetes. On average, this increased the postoperative lactate concentration at any level by 20% compared to non-diabetics.

N=488		Univariate Analysis	Multivariate Analysis	
Factor		P-value	Coef +/- SD	P-value
Age		0.246*		0.925
Gender		0.012*		0.129
Pathology	Benign v Primary	0.442		0.144
	Primary v Secondary	0.226*		0.878
Liver directed chemotherapy		0.129*		0.219
Open or laparoscopic resection		0.009*		0.611
Radiofrequency ablation		0.191*		0.402
Wedge resection included		<0.001*		0.086
Bile duct reconstruction		0.004*		0.651
Number of segments resected		<0.001*	0.143±0.012	<0.001†
Synchronous bowel procedure		0.516		
Surgeons assessment of liver		<0.001*	0.185±0.042	<0.001†
Redo operation	1st v 2nd resection	0.268		
	2nd v 3rd resection	0.654		
Preoperative diabetes		<0.001*	0.204±0.064	0.002†
Body Mass Index		0.06*		0.905
ASA Grade	1 vs. 2	0.014*		0.824
	2 vs. 3	0.709		0.872
Physiologic score		0.054*		0.221
Hepatic fibrosis/cirrhosis		0.667		
Preoperative bilirubin		0.320		
Preoperative haemoglobin		0.633		
Neutrophil:lymphocyte ratio		0.400		
Preoperative albumin		0.399		
Preoperative alkaline phosphatase		0.014*		0.775
Preoperative creatinine		0.392		
Preoperative Glomerular Filtration Rate (GFR) >90ml/min		0.042*		0.054
Blood loss (ml)	<500 v 500-999	<0.001*	0.131±0.038	0.013†
	500-999 v >1000	0.435		0.884
Units of red cells transfused		<0.001*	0.043±0.011	<0.001†

Table 7.6 Univariate and Multivariate analysis of pre- and intraoperative factors associated with serum lactate concentration following liver resection in 488 patients.

*** Significant at the level of 0.25 for univariate analysis and included in multivariate analysis**
†Significant at the level of 0.05 for multivariate analysis

7.5 Discussion

The principal findings of this study are that higher initial serum lactate concentration after liver resection is associated with an increased risk of post-operative mortality and renal and liver dysfunction. Both the 90-day mortality rate and the rate of renal dysfunction in patients with initial lactate concentrations greater than 6mmol/L were 28% compared to those patients with initial lactate concentrations less than 2mmol/L where they were 0.7% and 2.2% respectively. Similarly, higher lactate concentration was associated with higher postoperative peaks in serum bilirubin concentration and PT, as well longer lengths of hospital stay.

These findings support and extend those of an earlier study[323] by demonstrating the association of post-operative lactate with renal and hepatic dysfunction and length of hospital stay in addition to mortality. Pre-operative diabetes mellitus, the surgeon's assessment of the liver at laparotomy, the extent of liver resection, blood loss and the number of units of blood transfused are also shown to be associated with post-operative serum lactate concentration.

During cellular hypoxia pyruvate is diverted from the citric acid cycle and converted to lactate, reducing the amount of ATP generated. This occurs in all metabolically active tissues including muscle, gut, liver , brain, erythrocytes and skin[324–326] and is exacerbated by intra-operative stresses including blood loss[325], endogenous release of stress hormones[327] and administration of pressor agents[328]. Liver ischaemia induced by handling of the liver during surgery and temporary inflow occlusion has been shown to lead to a rise in lactate[329]. Serum lactate can also be increased by transfusion of stored blood,

which contains a higher concentration of lactate than fresh blood depending on length of storage[330]. Administration of Hartmann's solution has been shown to have a small effect on serum lactate concentration[331]. A potential weakness of this study is that details of pressor agents were not recorded which could affect the lactate concentration. Similarly, precise details regarding intravenous fluid type and volume of fluid (colloid and crystalloid) were not recorded.

In addition to being a potential source of lactate the liver is the principle location of lactate metabolism, where it is converted back to glycogen, accounting for 70% of whole body lactate clearance[325]. No change in lactate metabolism has been demonstrated following recovery from partial hepatectomy in either rats [117] or humans[114], implying that the liver has a large functional reserve under physiological conditions of lactate production. However, the effects of intra-operative stress on hepatic glucose homeostasis have not been assessed, particularly when in combination with an extended hepatectomy. It is possible that inflow occlusion during resection and intra-operative handling of the liver lead to a temporary impairment of the ability of the liver to metabolise lactate. The finding of an association between the number of liver segments resected and the initial post-operative lactate supports this hypothesis. Diabetes is also known to be associated with impaired lactate metabolism via gluconeogenesis[325] and may account for the strong association with post-operative lactate in this series. Furthermore the use of metformin in non-insulin dependent diabetes has also been shown to increase lactate concentration[332]. The rise in serum lactate at the end of liver resection therefore may be due to a failure of lactate metabolism in addition to increased production during surgery.

Significantly the use of pre-operative chemotherapy was not shown to be associated with elevation of post-operative lactate. This may be due to a policy of allowing a period of recovery after completion of pre-operative chemotherapy before undertaking surgery. Interestingly the operating surgeon's assessment of the liver parenchyma was associated with the post-operative lactate concentration. This finding suggests that patient comorbidity was a more common cause of abnormal liver parenchyma than the use of liver-directed chemotherapy.

An important observation of this study is the relative rarity of major hepatic dysfunction following liver resection in this series with only one patient fulfilling the '50-50' criteria[186], who subsequently recovered. Despite the infrequency of major disturbances of post-operative bilirubin and PT there was an independent association with increasing concentration of post-operative lactate, demonstrating that even a minor degree of liver injury can lead to impaired lactate clearance or increase its production.

Renal dysfunction was also rare in this series, affecting 34 patients (7%) compared to 15% in a similar series[188]. The risk factors for post-operative renal dysfunction are likely to be similar to those in other forms of abdominal surgery, including blood loss and sepsis, which are also initiating factors for anaerobic metabolism and lactate production. This supports the value of initial lactate as an early predictor of renal dysfunction. Of note the risk of renal dysfunction appeared to rise more rapidly when the post-operative lactate rose above 5mmol/L (Figure 7.2). This suggests that the kidneys can tolerate a degree of oxidative stress to a threshold level beyond which the risk of damage rises rapidly.

There was a weak association between initial lactate concentration and length of hospital stay in the study (Table 7.4). However, this may also be affected by other factors such as postoperative complications, particularly bile leaks, and degree of social support.

The strongest association demonstrated was between lactate concentration and the risk of mortality. In a similar manner to renal dysfunction there seems to be a threshold level of post-operative lactate of approximately 6mmol/l above which the risk of 90-day mortality rises rapidly (Figure 7.3). Organ dysfunction was a major contributor to mortality in the series and initial lactate concentration is a valuable global marker of poor organ function in the early post-operative period, including cardiovascular, renal and hepatic dysfunction.

7.6 Conclusions

These findings are of value in clinical practice as it may be possible to use the initial post-operative lactate concentration to determine the patient pathway in the early post-operative period. Patients with an initial post-operative lactate of less than 2mmol/L have low rates of mortality and organ dysfunction and may not require post-operative critical care. In addition, the correlation of post-operative lactate with subsequent organ dysfunction and mortality may allow its use as a single measure of the impact of innovations in operative technique or peri-operative care.

Chapter 8: Renal dysfunction is an independent risk factor for mortality after liver resection and the main determinant of outcome in post-hepatectomy liver failure.

Wiggans MG, Shahtahmassebi G, Bowles MJ, Aroori S, Stell DA. (2013) Renal Dysfunction Is an Independent Risk Factor for Mortality after Liver Resection and the Main Determinant of Outcome in Posthepatectomy Liver Failure. *HPB Surg* 2013:875367.

DOI: 10.1155/2013/875367

8.1 Abstract

Introduction

The aim of this study was to assess the interaction of liver and renal dysfunction as risk factors for mortality after liver resection.

Methods

A retrospective analysis of 501 patients undergoing liver resection in a single unit was undertaken. Post-hepatectomy liver failure (PHLF) was defined according to the International Study Group of Liver Surgery (ISGLS) definition (assessed on day 5) and renal dysfunction according to RIFLE criteria. 90-day mortality was recorded.

Results

Twenty-three patients died within 90 days of surgery (4.6%). The lowest mortality occurred in patients without evidence of PHLF or renal dysfunction (2.7%). The mortality rate in patients with isolated PHLF or renal dysfunction

was 20% compared to 45% in patients with both. Diabetes (P=0.028), renal dysfunction (P=0.030) and PHLF on day 5 (P=0.011) were independent predictors of 90-day mortality.

Discussion

PHLF and postoperative renal dysfunction are independent predictors of 90-day mortality following liver resection but the predictive value for mortality is significantly higher when failure of both organ systems occurs simultaneously.

8.2 Introduction

Despite advances in both operative technique and peri-operative care liver resection is associated with mortality rates of 0 to 22% (median 3.7%) and morbidity rates of 12.5% to 66% (median 36%)[136] including liver[186,313] and renal dysfunction[140]. Liver dysfunction is a major contributor to both morbidity and mortality with an incidence between 1.2% and 32% in published series[137–139,172,181–184]. Renal dysfunction has also been shown to be associated with mortality following liver resection[188], with a reported incidence between 5 and 15%[140,141]. Post-hepatectomy renal failure may occur in conjunction with liver failure when maldistributive circulatory changes occur causing intravascular hypovolaemia[140,190], but is also related to operative stress and blood loss[148,152].

Post-operative liver dysfunction has been defined by the “50-50 criteria” as a prothrombin index of less than 50% (mean normal prothrombin time (PT) divided by patient's observed PT) and a serum bilirubin of >50µmol/L on the fifth postoperative day, which has been shown to predict liver failure and death after hepatectomy[186]. More recently post-hepatectomy liver failure (PHLF) and has

been defined by the International Study Group of Liver Surgery (ISGLS) as a postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinaemia on or after postoperative day five[187]. The ability of this newer definition of PHLF, using lower measures of dysfunction, to predict mortality has not been thoroughly assessed.

The aim of this study was to assess the utility of the ISGLS definition of PHLF on postoperative day 5 as a predictor of mortality and to determine the interaction of liver and renal dysfunction in predicting 90-day mortality after liver resection.

8.3 Methods

A retrospective analysis of a prospectively maintained database of all patients undergoing liver resection in this unit between July 2005 and September 2012 was undertaken. Five hundred and one patients were studied. Patient characteristics, laboratory data and intra-operative details were retrieved. Liver resections were defined according to the Brisbane classification[17] and undertaken using standard techniques. Prior to resection the operating surgeon makes a visual assessment of the condition of the liver parenchyma and records this as normal or abnormal. Hepatic inflow occlusion was used in a minority of cases where there was excessive blood loss. The POSSUM scoring system was used to calculate the pre-operative physiological risk score[297].

All patients were followed up for a minimum of 90 days and mortality was recorded along with details of the cause of death. The cause of death was determined from case-sheet review, radiological and laboratory data and from death certificates. Patients who died with jaundice and/or radiological evidence of ascites and/or encephalopathy in the absence of any other clear diagnosis were determined to have died of liver failure. Patients who died within 24 hours of surgery were excluded from further analysis as these deaths were most likely due to peri-operative complications. Patients were also excluded if no postoperative blood tests were available.

Serum biochemistry tests and coagulation assays were performed on patients in the first 24 post-operative hours and the tests repeated according to clinical course. The peak measurement of bilirubin, prothrombin time (PT) and creatinine were recorded and used for analysis and patients with PHLF were identified as having an increased PT and serum bilirubin on postoperative day five according to the ISGLS definition [187]. In patients with preoperatively increased PT or serum bilirubin concentration PHLF was defined as an increasing serum bilirubin concentration and increasing PT on postoperative day 5 compared with the values of the previous day. Renal dysfunction was defined as an increase in serum creatinine of ≥1·5-fold from the preoperative baseline within the first five post-operative days, according to RIFLE criteria[298].

To determine potential associations between patient characteristics, operative factors and organ dysfunction with 90 day mortality univariate logistic regression or chi-square test at the level of $P<0.25$[229] was performed, as appropriate. Significant variables in the univariate analysis were included in the multivariate logistic regression model and were considered to be significant if $P<0.05$.

Mortality ratios for organ failure were calculated as the proportion of deaths to proportion of survivors. All analyses were carried out using the statistical package R 2.1.14[230].

8.4 Results

Five-hundred and one patients were studied. The indications for surgery, pre-operative and operative details are shown in Table 8.1. Two patients who died within 24 hours of surgery were excluded from further analysis. One patient died of heart failure after a partially extended right hepatectomy and one died of biliary sepsis and multi-organ failure following an extended right hepatectomy for hilar cholangiocarcinoma.

N=501			Median (Range)	Count (%)
Age			65 (21-90)	
Gender	Female			223 (45)
	Male			278 (55)
Histological diagnosis	Benign			46 (9)
	Primary	Hepatocellular carcinoma		39 (8)
		Cholangiocarcinoma		31 (6)
		Others		28 (6)
	Secondary	Colorectal metastases		308 (61)
		Other metastases		49 (10)
Liver directed chemotherapy	Yes			176 (35)
	No			325 (65)
Diabetes	Yes			55 (11)
	No			446 (89)
BMI			26 (16-54)	
ASA Grade	1			51 (10)
	2			323 (64)
	3			124 (25)
	4			2 (0.4)
	Not recorded			1 (0.2)
Physiologic risk score			16 (12-32)	
Operative risk score			24 (14-35)	
Estimated P-Possum mortality (%)			7.7 (0.9-69.3)	
Confirmed fibrosis/cirrhosis	Yes			22 (4)
	No			479 (96)
Preoperative bilirubin (µmol/L)			9 (2-162)	
Preoperative haemoglobin (g/dL)			13.2 (8.6-17.0)	
Preoperative white cell count (/L)			6.9 (2.7-25.0)	
Preoperative albumin (g/L)			44 (24-53)	
Preoperative alkaline phosphatase (U/L)			95 (34-1190)	
Preoperative creatinine (µmol/L)			78 (40-430)	
Preoperative Glomerular Filtration Rate (GFR)	>90ml/min			163 (33)
	<90ml/min			326 (65)
	Not measured			12 (2)
Preoperative neutrophil lymphocyte ratio (NLR)			2.5 (0.3-17.3)	
NLR >5	Yes			59 (12)
	No			442 (88)
Open or laparoscopic approach	Open			453 (90)
	Laparoscopic			48 (10)
Radio frequency ablation (RFA) included	Yes			23 (5)
	No			478 (95)
Wedge resection included	Yes			189 (38)
	No			312 (62)

Table 8.1 Preoperative and intraoperative characteristics of 501 patients undergoing hepatic resection between July 2005 and September 2012

Table 8.1 continued.

N=501		Median (Range)	Count (%)
Operation	Right hemihepatectomy		173 (35)
	Extended right hemihepatectomy		34 (7)
	Left hemihepatectomy		64 (13)
	Extended left hemihepatectomy		17 (3)
	Left lateral sectorectomy		48 (10)
	Wedge resection only		133 (27)
	Other		32 (6)
Bile duct reconstruction included	Yes		46 (9)
	No		455 (91)
Synchronous bowel procedure	Yes		23 (5)
	No		478 (95)
Operation number	1st resection		465 (93)
	2nd resection		31 (6)
	3rd resection		5 (1)
Number of segments resected		4 (1-6)	
Number of procedures		1 (1-10)	
Surgeon's assessment of liver parenchyma	Normal		323 (64)
	Abnormal		171 (34)
	Not recorded		7 (1)
Blood loss	<500ml		246 (49)
	500-999ml		175 (35)
	≥1000ml		76 (15)
	Not recorded		4 (0.8)
Units transfused		0 (0-26)	

Details of twenty-one patients (4.6%) who died within 90 days of surgery are shown in Table 8.2. There was no significant difference in the median age of patients who died (71 years) and those who survived (65 years). The median interval to death after surgery was 31 days (7-89 days).

Cause of death	Count	Gender		Age	Right hepatectomy	Extended right	Extended left	Minor resection	Interval to death (days)
		Male	Female						
Liver failure	11	9	2	67 (58-76)	3	7	1	0	31 (11-83)
Malignancy	4	2	2	58 (43-76)	2	1	0	1	68.5 (14-86)
Sepsis	1	1	0	71	0	1	0	0	15
PE	1	1	0	71	1	0	0	0	7
Anastomotic leak	1	1	0	80	0	0	0	1	8
Peptic ulcer	1	0	1	81	1	0	0	0	22
Strangulated hernia	1	1	0	76	0	0	0	1	89
Peritonitis	1	1	0	76	0	0	0	1	70

Table 8.2 Details of 21 patients who died within 90 days of surgery performed between July 2005 and September 2012 Two patients who died within 24 hours of surgery were excluded

Of the 499 patients studied, blood tests were available in 495 patients (99.2%). Four patients did not have post-operative blood tests, all of whom had minor resections (fewer than three segments) and none of whom died within the study period and were excluded from analysis. It was not necessary to administer clotting factors to any surviving patients between postoperative days (POD) 1-5. A summary of liver and renal function tests in the whole cohort is shown in Table 8.3 along with the associated mortality.

Laboratory parameters at day 5 (N=495)	Count (%)	90-day mortality (%)	Death due to liver failure
No PHLF or renal dysfunction	444 (89.7)	12 (2.7)	4
PHLF alone	20 (4.0)	2 (10)	2
Renal dysfunction alone	20 (4.0)	2 (10)	2
Renal dysfunction plus PHLF	11 (2.2)	5 (45.5)	3

Table 8.3 Postoperative liver and renal dysfunction in 495 patients undergoing hepatic resection between July 2005 and September 2012

PHLF occurred in 31 patients of whom two had pre-existing liver failure and 12 had extended resections. Seven patients in this group died within 90 days of surgery. Renal dysfunction also occurred in 31 patients, of whom 11 had extended resections. Seven patients in this group died within 90 days of surgery. Among 55 patients with diabetes mellitus renal dysfunction occurred in seven patients (12.7%) compared to 24 of 440 patients without diabetes (5.5%) (P=0.067). There was no significant difference in the number of diabetic patients who developed postoperative renal dysfunction between those with normal preoperative renal function (0/12) and those with impaired preoperative renal function (7/43) (P=0.326).

The lowest mortality (2.7%) occurred in the 444 patients without laboratory evidence of PHLF or renal dysfunction at day five, of whom 12 died, compared to 9 of 51 (17.6%) patients with either or both of these diagnoses. In the first group four of the twelve deaths were due to liver failure compared to seven of the nine deaths in the group with evidence of organ dysfunction at POD 5.

The mortality rate in patients who fulfilled the criteria for PHLF on POD 5 but did not have renal dysfunction was identical (2 of 10 patients) to that of patients with renal dysfunction without PHLF (2 of 10 patients). All four of these patients died of liver failure. Mortality was greatest in the group of eleven patients with both PHLF and renal dysfunction of whom five died. Three of these five patients died of liver failure, one from anastomotic leak and one from a bleeding peptic ulcer.

Multivariate analysis of potential risk factors for mortality including postoperative organ dysfunction (Table 8.4) revealed that the only preoperative factor independently associated with 90-day mortality was the presence of diabetes (P=0.028), which more than trebled the risk of 90-day mortality.

N=495		Univariate		Multivariate	
Factor (Pre-operative and operative factors and postoperative blood tests)		**Coefficient (95% CI)**	**P-value**	**Coefficient (95% CI)**	**P-value**
Age		1.05 (1.01-1.10)	0.029*		0.194
Gender		2.36 (0.91-6.08)	0.077*		0.196
Pathology			0.274		
Liver directed chemotherapy			0.356		
Diabetes		3.09 (1.16-8.20)	0.024*	3.41 (1.14-10.23)	0.028**
BMI			0.444		
ASA grade	1 vs 2	3.02 (0.70-13.11)	0.139*		0.678
	2 vs 3		0.724		
Physiologic score		1.12 (1.03-1.22)	0.010*		0.544
Operative score			0.303		
P-Possum mortality		1.04 (1.01-1.07)	0.010*		0.479
Fibrosis/cirrhosis			0.986		
Preoperative bilirubin		1.01 (1.00-1.03)	0.081*		0.652
Preoperative haemoglobin		0.71 (0.55-0.93)	0.012*		0.195
Preoperative white cell count			0.388		
Preoperative albumin		0.90 (0.84-0.96)	0.002*		0.168
Preoperative alkaline phosphatase			0.884		
Preoperative creatinine		1.01 (1.00-1.02)	0.098*		0.764
Preop neutrophil lymphocyte ratio		1.13 (0.98-1.31)	0.086*		0.366
Preop neutrophil lymphocyte ratio >5		2.18 (0.78-6.11)	0.138*		0.345
Open or laparoscopic resection			0.987		
Radiofrequency ablation (RFA) included			0.991		
Wedge resection included			0.588		
Bile duct reconstruction included		2.96 (1.05-8.39)	0.041*		0.383
Synchronous bowel procedure			0.346		
Operation number			0.549		
Number of segments resected		1.59 (1.18-2.14)	0.003*		0.075
Number of procedures			0.786		
Surgeons assessment of liver parenchyma		2.14 (0.92-4.96)	0.076*		0.494
Blood loss (ml)	<500 vs. >500	2.67 (1.27-5.61)	0.009*		0.716
	>500 vs. >1000		0.652		
Units of red cells transfused		1.13 (1.02-1.26)	0.023*		0.224
PHLF at POD 5		1.02 (1.01-1.03)	<0.001*	4.51 (1.42-14.40)	0.011**
Renal dysfunction (Creatinine rise >1.5x)		1.02 (1.01-1.03)	<0.001*	3.63 (1.13-11.66)	0.030**

Table 8.4 Univariate and multivariate analysis of pre- and operative factors as well postoperative blood tests associated with 90-day mortality following liver resection in 495 patients

***Significant at the level of 0.25 for univariate analysis and included in multivariate analysis. **Significant at the level of 0.05 for multivariate analysis**

Both PHLF on POD 5 and post-operative renal dysfunction were independently associated with 90-day mortality. PHLF at POD 5 increased the risk of 90-day mortality by a factor of 4.5 (P=0.011) and renal dysfunction increased the risk by a factor of 3.6 (P=0.030).

The positive predictive value (PPV) for mortality in patients who fulfilled the criteria for PHLF (including those with and without renal dysfunction) was 22.6%. However, within this group the PPV was much lower (10%) if the criteria for PLF were fulfilled with normal renal function (Table 8.5). The PPV for mortality of fulfilling the criteria for PHLF with concurrent renal dysfunction was 45%.

	Positive Predictive Value (PPV)	**Negative Predictive Value (NPV)**
No PHLF or renal dysfunction	0.027	0.824
PHLF alone	0.1	0.970
Renal dysfunction alone	0.1	0.970
PHLF and renal dysfunction	0.455	0.967

Table 8.5 Predictive values for 90-day mortality of PHLF and renal dysfunction within first five post-operative days in 495 patients undergoing liver resection

The effect of developing renal dysfunction in the context of PHLF is demonstrated by the greater than four-fold increase in mortality ratio (Figure 8.1).

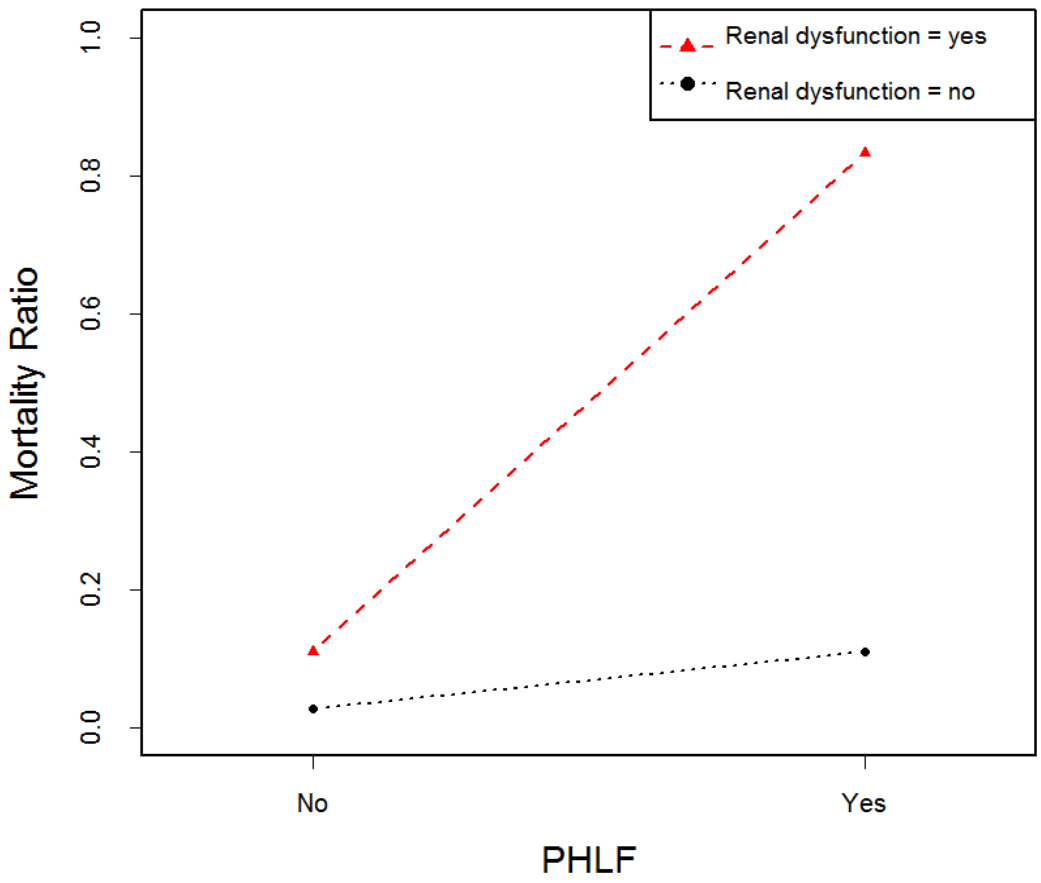


Figure 8.1 Mortality ratio of combined liver and renal dysfunction in 495 patients undergoing liver resection

8.5 Discussion

The principle findings of this study are that PHLF on POD 5 as defined by the ISGLS and postoperative renal dysfunction are independent predictors of 90-day mortality following liver resection. The predictive value for mortality is significantly higher when failure of both organs occurs, with a PPV of 45% and NPV of 97%. Preoperative diabetes mellitus is also an independent predictor of 90-day mortality.

The 90-day mortality (4.6%) in this series is similar to results of other units [136]. An important observation is that half the post-operative deaths in the series occurred between 31 and 90 days after surgery, stressing the importance of reporting 90-day rather than 30-day mortality. Of the 21 post-operative deaths 11 were found to be due to liver failure.

The study confirms the ability of PHLF to predict 90-day mortality. Interestingly most patients who developed PHLF at POD 5 (24 of 31) recovered whilst six of the eleven patients who died of liver failure did not fulfil the ISGLS definition of PHLF at POD 5. Only one patient in this series fulfilled the “50-50 criteria” of post-operative liver dysfunction, who subsequently recovered. Therefore, the “50-50” criteria had no value as a predictor of liver failure or mortality in this series with a PPV of zero. In comparison, the ISGLS definition of PHLF has lower thresholds for abnormal bilirubin and PT and is a more clinically useful tool for the prediction of 90-day mortality with a PPV of 23% and NPV 97%. This is similar to the findings of the only other study to address this issue, which revealed the PPV and NPV of PHLF were 32% and 98% respectively[333]. Simple blood tests therefore have a low positive predictive value for mortality due to liver failure.

Renal dysfunction occurred in 6.3% of patients which is similar to other published series[140,141]. Renal dysfunction following liver resection may occur as a consequence of liver failure and hepato-renal syndrome, but may also result from hypovolaemia or damage from inflammatory mediators during surgery[140]. This occurs more commonly in elderly patients with atherosclerosis or hypertension[190]. These mechanisms of renal dysfunction may occur simultaneously. The use of low central venous pressure (CVP) during resection

may also increase the risk of postoperative renal dysfunction[334,335]. The results of this study demonstrate that isolated renal dysfunction is a significant risk factor for mortality independent of the development of PHLF. Interestingly the two patients with isolated renal dysfunction in the first-five post-operative days subsequently died of liver failure. This may be attributed to renal dysfunction delaying the onset of hepatic regeneration[336]. The most marked mortality effect of renal dysfunction was seen in conjunction with PHLF, where the mortality rate increased by a factor of four. Therefore, although the ISGLS definition of PHLF is able to predict mortality due to liver failure the development of renal dysfunction in this context is the single most important predictive factor.

The finding of the significance of diabetes as a risk factor for post-operative mortality confirms earlier findings[337]. Insulin is important for hepatic function and regeneration[338] and diabetes is also a risk factor for the development of non-alcoholic fatty liver disease and cirrhosis[339] which may lead to higher rates of PHLF[283]. Diabetic nephropathy is also a major cause of renal dysfunction[310].

In conclusion, we have demonstrated that PHLF as defined by the ISGLS on postoperative day five and postoperative renal dysfunction are able to predict 90-day mortality following liver resection, although most patients fulfilling these criteria of organ dysfunction will recover. In addition, many patients will succumb to liver failure without fulfilling the PHLF criteria in the early post-operative period. The combination of these two markers of organ dysfunction is the best early predictor of mortality following liver resection and we suggest that PHLF and postoperative renal dysfunction should be used in conjunction when predicting mortality after liver resection. Clinicians should use these findings to better assess the postoperative course for patients undergoing liver resection

and this information can be used when discussing progress with patients and their relatives.

Chapter 9: Extended pathology reporting of resection specimens of colorectal liver metastases-the significance of a tumour pseudocapsule

Wiggans MG, Shahtahmassebi G, Malcolm P, McCormick F, Aroori S, Bowles MJ, Stell DA. (2013) Extended pathology reporting of resection specimens of colorectal liver metastases: the significance of a tumour pseudocapsule. *HPB (Oxford)* 15:687–94.

DOI: 10.1111/hpb.12028

9.1 Abstract

Introduction

The aim of this study was to analyse the relative influence of factors reported in the minimum histopathology dataset for colorectal liver metastases (CRLM) and other pre-operative factors compared to additional data relating to the presence of tumour pseudocapsules and necrosis on tumour recurrence one year after resection.

Methods

Extended histological reporting of liver specimens for CRLM was performed for a period of fourteen months and included the presence of pseudocapsules and necrosis in each tumour. Details of tumour recurrence were obtained from surveillance imaging.

Results

In sixty-six patients there were twenty-seven recurrences within one year. Recurrence was associated with a positive resection margin and the absence of a pseudocapsule ($p<0.05$). Pseudocapsules were associated with younger age, nodal stage of the primary colorectal tumour and metachronous tumours. The association between a pseudocapsule and lower early recurrence occurred in patients with synchronous metastases.

Discussion

These findings demonstrate that histological examination of resection specimens can provide significant additional prognostic information for patients after resection of CRLM, compared to clinical and radiological data available pre-operatively. Our finding that the absence of a pseudocapsule in patients with synchronous CRLM is associated with a dramatically worse outcome may help direct patient-specific adjuvant treatment and care.

9.2 Introduction

Although resection of colorectal liver metastases (CRLM) offers overall five year survival rates ranging from 32-65%[40,41] there is a spectrum of outcomes following surgery with some individuals remaining disease free and potentially being cured, while others will recur early with a poor outcome[340,341]. A number of risk scoring systems exist to stratify patients according to likely five-year survival. These systems predominantly use factors measurable pre-operatively which have been shown to be markers of prognosis, such as Carcinoembryonic Antigen (CEA) estimation[236], tumour number[236–239,342–348], tumour size[236,238,239,342,348], resection margin clearance[236–238,240,241,345,346,349–351], the presence of satellite lesions[241] and the ratio of neutrophils to lymphocytes amongst white cells in a full blood count measured pre-operatively[168]. Liver specimens are routinely sent for pathological analysis after resection and the UK Royal College of Pathologists (RCPath) minimum dataset for liver specimens with colorectal metastases includes details of tumour number, size, location, resection margin clearance, capsular invasion, degree of differentiation, the presence of tumour necrosis, vascular and lymphatic invasion, the presence of satellite lesions, invasion of adherent tissue, and lymph node status if sampled[122]. With regards to prognostic factors, the most important additional information the pathology report reveals which is not available pre-operatively is the resection margin status. However, of the fifteen risk scoring systems available, only three have shown the presence of an involved resection margin to be a significant prognostic factor[352]. Therefore, histological examination of CRLM specimens may add relatively little additional

prognostic information compared to clinical, radiological and laboratory data in the currently used scoring systems.

Extended examination of resection specimens may reveal other features whose prognostic significance has not been rigorously assessed, including details of a fibrous pseudocapsule around the tumour and the degree of tumour necrosis. The presence of a pseudocapsule has been associated with better overall survival after resection of CRLM[123–125]. Tumour necrosis can result from chemotherapy use[126] and is also seen in tumours with high rates of cellular turnover in rapidly expanding tumours[127]. Therefore, tumour necrosis may be associated with more aggressive tumours and a worse prognosis.

The aim of this study was to analyse the relative significance of factors reported in the minimum histopathology dataset and other pre-operative factors compared to additional data relating to the presence of tumour pseudocapsules and necrosis on tumour recurrence one year after resection of CRLM.

9.3 Methods

Between March 2010 and May 2011, the Histopathology Department at Derriford Hospital performed extended reporting of CRLM specimens as an experimental protocol. Histology reports documented the presence or absence of a pseudocapsule, as well as how much of each tumour diameter was encompassed (zero, <50% or >50%). The presence and degree of necrosis observed in each tumour (nil, <33%, 33-66% and complete necrosis) was also recorded. Up to a maximum of the three largest tumours in each patient were

assessed and relevant features recorded. The pseudocapsule was identified as a paucicellular collagenous band present between the tumour cells and the adjacent hepatocytes, which measured at least 0.1mm in thickness (Figure 9.1). Tumour necrosis was characterised as discrete foci of cellular debris indicative of coagulative cell death (Figure 9.2). A proforma was designed and agreed within the Histopathology department to standardise reporting of resection specimens. In cases of heterogeneity between tumours the amount of pseudocapsule in up to the three largest tumours was measured and an average figure calculated according to a simple formula (>50% = 2, <50% = 1, no pseudocapsule = 0) and used in analyses. The amount of necrosis was determined for the largest lesion only.

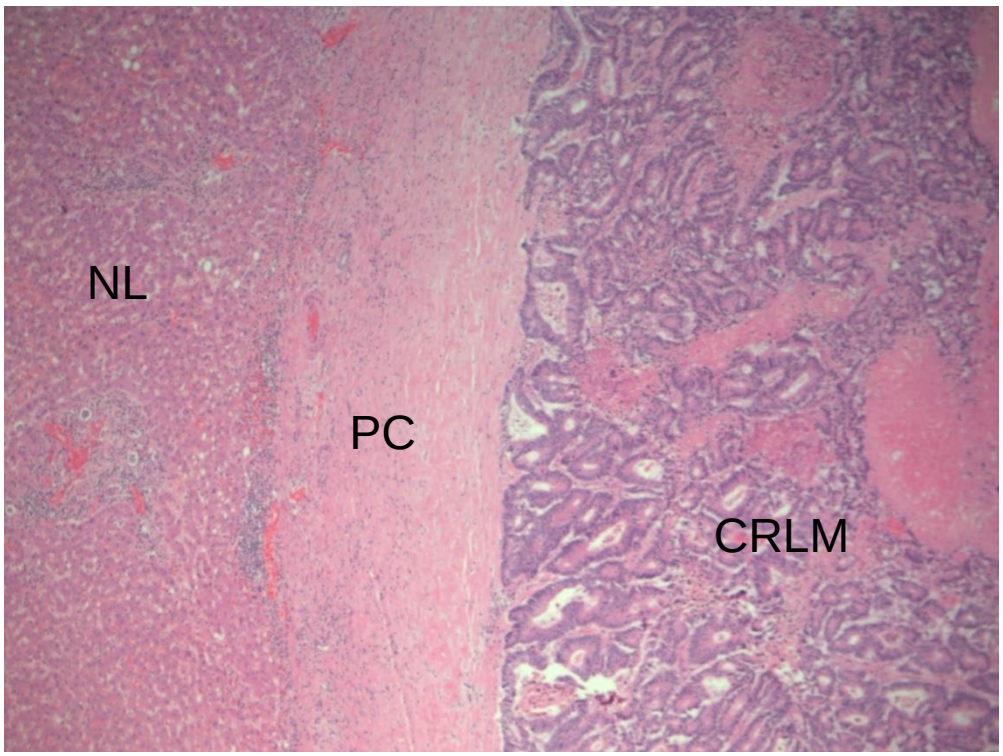


Figure 9.1 Pathological examination showing a pseudocapsule (PC), non-neoplastic liver (NL) and a colorectal liver metastasis (CRLM). Original magnification x50 using Haematoxylin and Eosin stain

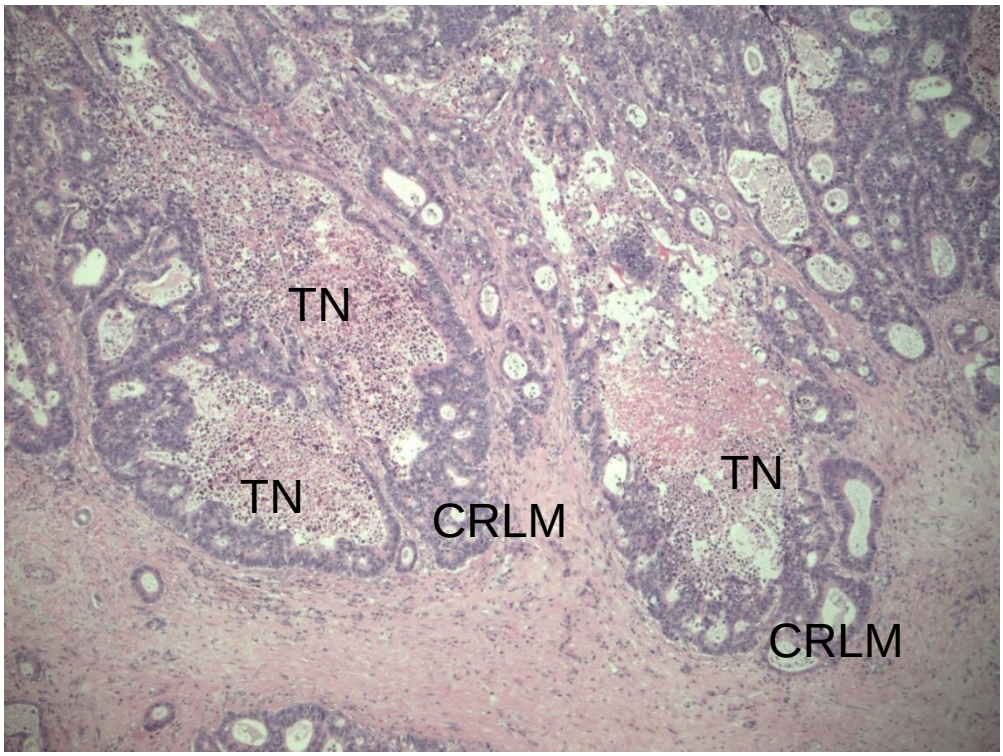


Figure 9.2 Pathological examination showing tumour necrosis (TN) in colorectal liver metastases (CRLM). Original magnification x50 using Haematoxylin and Eosin stain

All patients underwent tumour staging with CT scan prior to surgery. In addition, 46 patients had a pre-operative MRI scan and 50 patients a pre-operative PET scan, at the discretion of the referring clinician.

A prospective database is maintained of all patients undergoing resection for CRLM and a review of these patients was performed when all had been followed up for a minimum of one year. The database holds information on primary histology, timing of detection of metastatic disease (synchronous tumours were defined as those discovered pre-operatively or within two months of primary surgery), the neutrophil to lymphocyte ratio, the use of chemotherapy as well as the histological features of the resected CRLM. Details of tumour recurrence were identified from surveillance imaging which is performed according to published guidelines [122]. CEA estimation was not used routinely in post-operative surveillance. One patient did not have surveillance imaging in the first post-operative year and was excluded from recurrence analysis. One year recurrence was chosen as the primary end point because a high proportion of CRLM recur within this timeframe and early recurrence is associated with worse overall survival[340,341].

Potential associations between one year tumour recurrence and clinical and histological characteristics were tested initially using univariate logistic regression or chi-square test at the level of $P < 0.25$[229], as appropriate. The association between clinical and histological characteristics and the presence of a tumour pseudocapsule in individual tumours was tested in a similar fashion. Significant variables in the univariate analysis were included in the multivariate logistic regression model and were considered to be significant if $P < 0.05$. All analyses were carried out using the statistical package R 2.1.14[230].

9.4 Results

Sixty-six patients were identified who underwent surgery for CRLM of whom 65 were available for recurrence analysis. Additional staging MRI scans were performed in 28 of 38 patients with synchronous tumours and 18 of 28 with metachronous tumours (P=0.431). Additional staging PET scans were performed in 28 of 38 patients with synchronous tumours and 22 of 28 with metachronous tumours (P=0.774). The median number of surveillance scans performed was one (1-4) in patients who recurred and two (1-5) in patients who had not recurred at one year.

In addition to surgery four patients had intra-operative radiofrequency ablation (RFA). Six patients died of recurrent cancer in the first year of follow-up. Twenty-eight patients (43.1%) developed recurrent cancer within the first year of follow-up. Eight of these recurred in the liver only, 12 had extrahepatic recurrence only and 8 had both hepatic and extrahepatic recurrence. Patient characteristics are displayed in Table 9.1.

N=66		Median (Range)	Count (%)
Age		65 (33-84)	
Gender	Male		40 (60.6)
	Female		26 (39.4)
Primary T stage	0		2 (3.0)
	1		3 (4.5)
	2		7 (10.6)
	3		29 (43.9)
	4		23 (34.8)
	Unavailable		2 (3.0)
Primary N stage	0		34 (51.5)
	1		18 (27.2)
	2		11 (16.7)
	Unavailable		3 (4.5)
Timing	Synchronous		38 (57.6)
	Metachronous		28 (42.4)
Liver-directed chemotherapy	Synchronous		35 (92.1)
	Metachronous		11 (39.2)
Neutrophil Lymphocyte Ratio	Less than 5		57 (86.4)
	More than 5		9 (13.6)

Table 9.1 Pre-operative details of 66 patients undergoing extended histological reporting of resection of hepatic colorectal metastases.

From the total patient group 132 lesions were examined histologically in the extended dataset. In two patients three tumours had responded completely to chemotherapy and were only identifiable microscopically as areas of complete necrosis. In these tumours, the presence of a pseudocapsule could not be assessed. Histological details of the resected specimens including the RCPath dataset and the presence of a pseudocapsule and degree of tumour necrosis for the 65 patients included in the recurrence analysis are shown in Table 9.2.

N=65		1-year recurrence			
		No (n=37)		Yes (n=28)	
		Median (Range)	Count	Median (Range)	Count
Number of lesions identified		2 (1-10)		3 (1-10)	
Max diameter at histology (mm)		27 (3-119)		43 (7-120)	
Satellite lesions	Yes (0)		0		0
	No (65)		37		28
Margin less than 10mm	Yes (45)		24		21
	No (20)		13		7
Margin less than 1mm	Yes (22)		9		13
	No (43)		28		15
Liver capsule smooth and intact	Yes (55)		33		22
	No (10)		4		6
Invasion of adherent tissue	Yes (1)		0		1
	No (64)		37		27
Differentiation	No tumour (3)		2		1
	Well/moderate (62)		35		27
Vascular invasion	Yes (9)		3		6
	No (56)		34		22
Histological evidence of response to chemotherapy	No response (4)		2		2
	Response (19)		13		6
	Uncertain (7)		4		3
	Not recorded (35)		18		17
Average amount of pseudocapsule	Nil (36)		17		19
	<50% (17)		12		5
	>50% (10)		7		3
	N/A (2)		1		1
Amount of necrosis of the largest tumour	Nil (4)		3		1
	<33% (29)		16		13
	33-66% (21)		13		8
	>66% (11)		5		6

Table 9.2 Histopathological features and 1-year recurrence of 65 patients undergoing extended histological reporting of resection of hepatic colorectal metastases with one year follow up.

In two patients (3 tumours) a complete response to chemotherapy was noted and therefore pseudocapsule could not be identified (N/A).

Heterogeneity in the presence of tumour pseudocapsules in multiple metastases was observed in 6 of 27 patients, where pseudocapsules were absent in some tumours, and in 5 of 27 patients where a differing amount of pseudocapsule was noted between tumours.

9.4.1 Analysis of factors associated with one-year recurrence in 65 patients.

Univariate analysis of pre-operative and histological factors and one-year recurrence revealed potential associations with age, number of metastases, a resection margin of less than one millimetre and the presence or absence of a pseudocapsule (P<0.250) (Table 9.3).

Factor (N=65)	Univariate P-value	Multivariate P-value	Incidence ratio (95% CI)
Age	0.025*	0.876	
Sex	0.506		
Max diameter of tumour at histology	0.323		
Number of lesions	0.240*	0.831	
Capsule smooth and intact	0.408		
Margin less than 1mm	0.109*	0.045**	2.89 (1.61– 5.18)
Margin less than 10mm	0.545		
Histological response to chemotherapy	0.674		
T stage of primary tumour	0.571		
N stage of primary tumour	0.381		
Synchronous vs. metachronous	0.824		
Liver directed chemotherapy (yes/no)	0.710		
Neutrophil Lymphocyte Ratio (>5)	0.320		
Pseudocapsule present	0.114*	0.030**	0.30 (0.174 - 0.524)
Necrosis of largest lesion	0.886		

Table 9.3 Univariate and Multivariate analysis of pre-operative and histological factors affecting 1-year recurrence after resection of hepatic colorectal metastases in 65 patients.

**** Significant at the level of 0.25 for univariate analysis and included in multivariate analysis***
*****Significant at the level of 0.05 for multivariate analysis***

Multivariate analysis revealed that only the absence of a pseudocapsule and a resection margin of less than one millimetre were significantly associated with early tumour recurrence (Table 9.3). One-year recurrence rates were lower for

patients with tumour pseudocapsules (8/27) than for patients with no pseudocapsule (19/36) (P=0.030). There was no significant difference in tumour recurrence rates according to the amount (< or >50%) of pseudocapsule present (P=0.750). (Figure 9.3). The recurrence rate in patients with a resection margin of <1mm was 13/22 compared to 15/43 in those with a margin of >1mm (P=0.045).

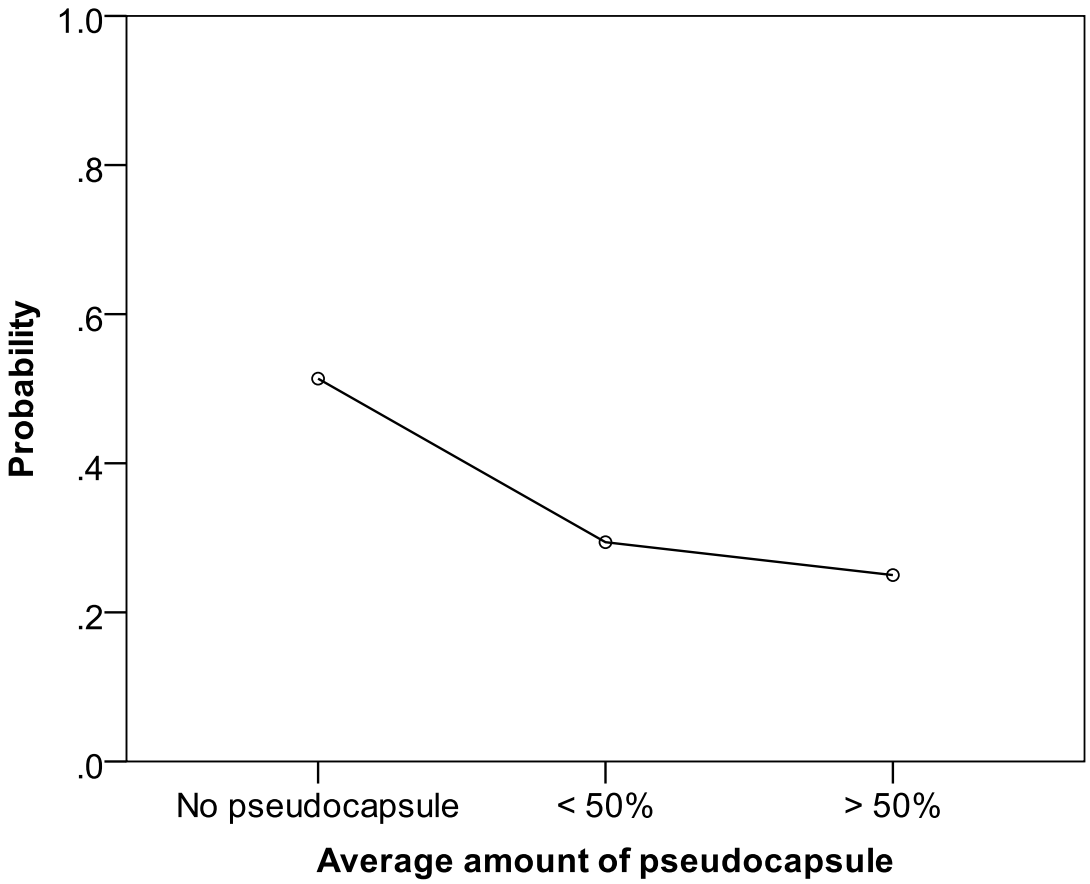


Figure 9.3 Probability of 1-year recurrence according to the amount of pseudocapsule present for 66 patients undergoing extended histological reporting of resection of hepatic colorectal metastases. No significant difference between <50% and >50% (P=0.75)

9.4.2 Analysis of factors associated with the presence of a pseudocapsule in 132 tumours.

Uni- and multivariate analysis was undertaken and revealed that increasing age, nodal status of the primary colorectal cancer and metachronous liver metastases were associated with the presence of a tumour pseudocapsule (Table 9.4).

Factor (N=132)	Univariate P-value	Multivariate P-value	Incidence ratio (95% CI)
Age (per year)	0.011*	0.005**	0.937 (0.90 - 0.98)
Sex	0.090*	0.142	
T stage of primary tumour	0.290		
N stage of primary tumour	<0.001*	0.025**	0.434 (0.24 - 0.77)
Metachronous vs. Synchronous	0.004*	0.004**	2.622 (1.13 - 6.09)
Neutrophil Lymphocyte Ratio	0.348		
Tumour size	0.167*	0.405	
Resection margin < 1mm	0.150*	0.105	

Table 9.4 Univariate and Multivariate analysis of factors associated with the presence of a tumour pseudocapsule (n=132) in 66 patients undergoing resection of hepatic colorectal metastases.

**** Significant at the level of 0.25 for univariate analysis and included in multivariate analysis***
*****Significant at the level of 0.05 for multivariate analysis***

The size of individual tumours was not associated with the presence of a pseudocapsule. For each year of age, the incidence of a pseudocapsule falls by0.073 (Figure 9.4).

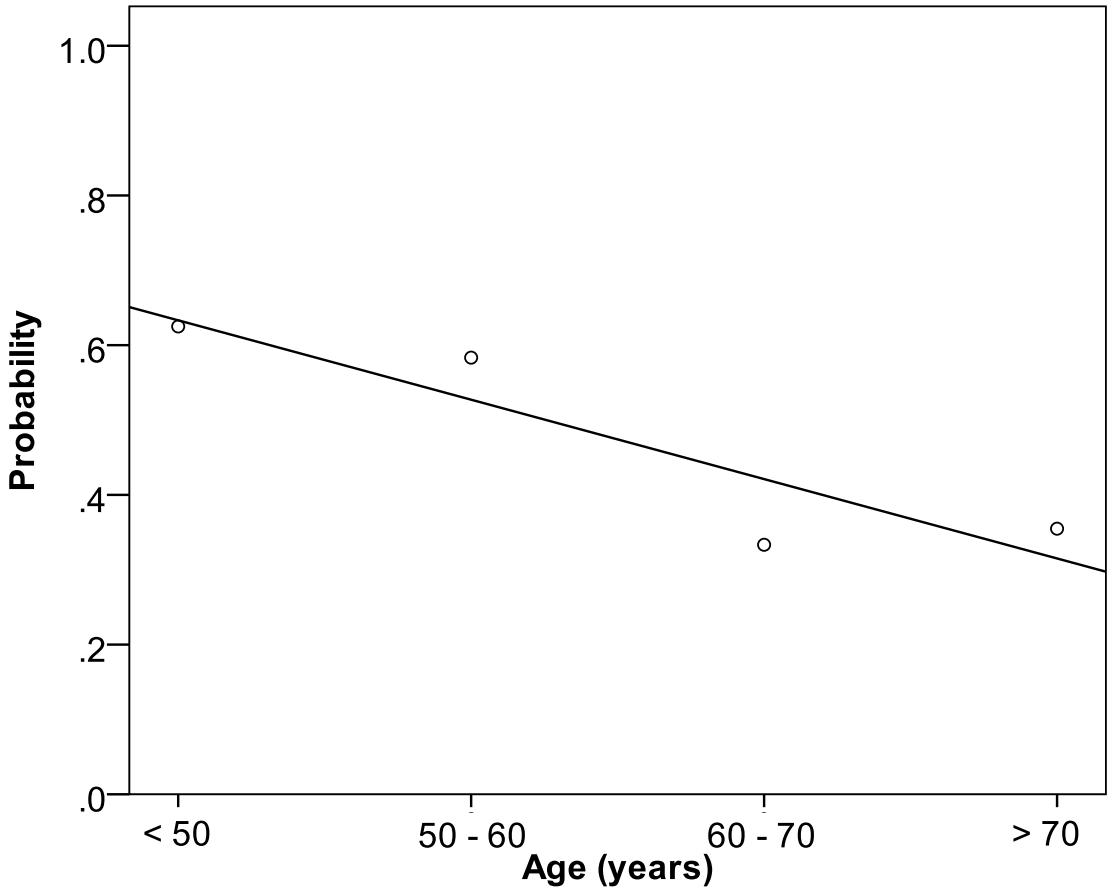


Figure 9.4 Probability of pseudocapsule presence according to age for 132 tumours in patients undergoing resection of hepatic colorectal metastases

Similarly, as the N stage increases by 1, the incidence of a pseudocapsule falls by 0.566 (Figure 9.5). Pseudocapsules occurred more commonly in tumours with a metachronous presentation (25/51) compared to a synchronous presentation (20/81) (P=0.004). Resection margin positivity was noted in 11 of 52 tumours with a pseudocapsule and 8 of 77 tumours without a pseudocapsule (P=0.105).

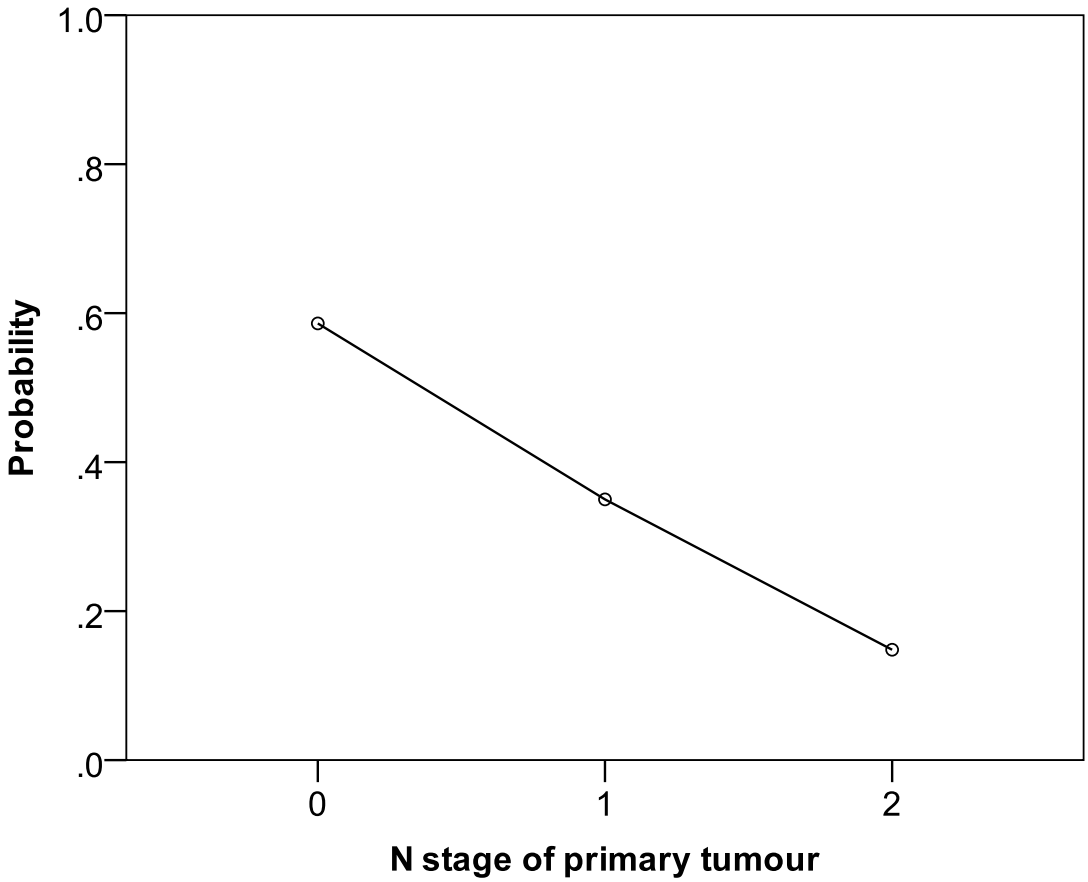


Figure 9.5 Probability of a pseudocapsule according to N stage of primary colorectal tumour for 132 tumours in patients undergoing resection of hepatic colorectal metastases.

The presence of a pseudocapsule had no significant association with one-year recurrence in patients with metachronous CRLM. However, in individuals with synchronous lesions the presence of a pseudocapsule was associated with a lower one-year recurrence rate (2/12 v 13/23) (P=0.026) (Table 9.5).

N=65				1-year recurrence		
				No	Yes	P-value
Timing	Synchronous (37)	Pseudocapsule	Absent (23)	10	13	0.026*
			Present (12)	10	2	
			N/A (2)	1	1	
	Metachronous (28)	Pseudocapsule	Absent (13)	7	6	0.521
			Present (15)	9	6	

Table 9.5 Relationship between pseudocapsule and 1-year recurrence in synchronous and metachronous lesions in patients undergoing resection of hepatic colorectal metastases.

Significant at the level of 0.05 on Fisher's exact test.

9.5 Discussion

The principal finding of this study is that a fibrous pseudocapsule is a common histological feature in patients undergoing resection of CRLM and is associated with a lower one-year tumour recurrence rate. This study extends earlier reports by showing that the benefit of a pseudocapsule occurs predominantly in patients with synchronous hepatic metastases. In these patients, only one third develop a pseudocapsule but have a dramatically reduced incidence of one-year tumour recurrence (2/12) compared to patients without a pseudocapsule (13/23). The study also confirms that the presence of an involved resection margin is an independent predictor of early tumour recurrence. These two findings demonstrate that histological examination of resection specimens can provide significant additional prognostic information for patients after resection of CRLM, compared to clinical and radiological data available pre-operatively.

The strength of the study lies in its prospective and unselected design, including all patients over a defined period with standardisation of reporting within predetermined guidelines. Specimens were reported by pathologists with a subspecialty interest in gastrointestinal disease who collectively approved the experimental protocol. The value of these findings to clinical practice is significant as the identification of a tumour pseudocapsule is readily performed on standard histology specimens without the need for special stains. A potential weakness of the study is that estimation of the extent of the pseudocapsule is subjective and semi-quantitative; however, our data show that the extent of the pseudocapsule is less important than its simple presence.

Although three previously published studies have shown that the presence of a pseudocapsule is associated with improved long-term survival after resection of CRLM[123–125] it is not commonly reported in this setting. Our series is the first to report lower recurrence rates in the presence of a tumour pseudocapsule in a Western population and adds further evidence of the benefit of adding this finding to the core data set in histology reporting of CRLM. Further follow-up will determine if lower early recurrence rates in this group are associated with improved survival.

It is not known what stimulates the formation of a fibrous pseudocapsule and what role it plays in preventing early recurrence. The capsule develops at the interface between tumour tissue and normal liver tissue and the proliferating stromal cells in the capsule have been shown to be myofibroblasts [125]. It has been suggested that CRLM activate hepatic stellate cells to form myofibroblasts and that this is a host defence response, similar to an inflammatory response,

creating a mechanical and chemical barrier around the tumour preventing further vascular and intrabiliary invasion[125]. Our finding that the absence of a tumour pseudocapsule is associated with a more aggressive primary tumour with nodal metastases supports this hypothesis, although we did not find any association with the neutrophil to lymphocyte ratio among circulating leucocytes, which has also been shown to be a marker of an inflammatory response to tumour[168]. It is also possible that older patients are less able to generate an inflammatory response to the tumour, accounting for the finding of a smaller proportion with tumour pseudocapsules in this age group.

Our finding that the absence of a pseudocapsule in patients with synchronous CRLM is associated with higher tumour recurrence may help direct patient-specific adjuvant treatment and care. For example, these patients may benefit from an increased frequency of postoperative imaging surveillance. Although postoperative chemotherapy following resection of CRLM has been shown to be of limited value[353], future trials of this modality may be developed to target treatment to high-risk groups, such as patients with synchronous tumours with no pseudocapsules.

Further research needs to be undertaken to confirm the potential association of a lower tumour recurrence rate in patients with tumour pseudocapsule in larger series, in addition to correlating this finding with improved survival. Further data may allow the development of a risk scoring system incorporating this finding. This may help clinicians and patients make informed decisions regarding post-operative surveillance as well as the use of postoperative chemotherapy.

9.6 Acknowledgements

Thanks to Dr N. Robertson and Dr J. Denson (Consultant Histopatholgists) for their work in performing extended reporting during this study.

Chapter 10: Influence of social-economic deprivation on likelihood of undergoing liver resection for hepatic colorectal metastases and outcome following surgery.

Wiggans MG, Shahtahmassebi G, Aroori S, Bowles MJ, Stell DA. (2014) Socioeconomic deprivation influences the likelihood of undergoing liver resection for colorectal liver metastases but not the outcome. *HPB (Oxford) 17:150–58.*

DOI:10.1111/hpb.12290

10.1 Abstract

Introduction

The aim of this study was to compare the socioeconomic profile of patients undergoing liver resection for colorectal liver metastases in a regional hepatopancreatobiliary unit with that of the local population. A further aim was to determine if degree of deprivation is associated with tumour recurrence after resection.

Methods

A retrospective analysis of patients undergoing liver resection for colorectal liver metastases was performed. Geodemographic segmentation was used to divide the population into five categories of socioeconomic status (SES).

Results

During a seven-year period 303 patients underwent resection for colorectal liver metastases. The proportion of patients in the two least deprived categories undergoing resection was greater than that of the local population (50.2% vs. 40.2%) and the proportion in the two most deprived categories was lower

(18.3% vs. 30.1%) (P<0.001). There was no difference in recurrence rate (P=0.867) or disease-free survival among categories of SES (P=0.913). Multivariate analysis demonstrated no association between SES and tumour recurrence (P=0.700).

Discussion

Liver resection for colorectal metastases is performed more commonly among the least socioeconomically deprived population than among the most deprived. However, degree of deprivation was not associated with tumour recurrence after resection.

10.2 Introduction

The incidence of primary colorectal cancer is associated with low socioeconomic status (SES) in the UK, where the age standardised incidence is 11% higher in men living in the most deprived areas of England compared with those living in the least deprived[132], although no difference has been demonstrated in women. Similar associations have been found in the USA, where individuals with higher levels of deprivation have been found to have a greater risk for the development of colorectal cancer even when other risk factors are controlled for[354]. Population studies have also shown that low SES is associated with worse outcome amongst patients with colorectal cancer[133–135]. Approximately a quarter of patients with colorectal cancer will develop colorectal liver metastases (CRLM) at the time of presentation[122] and a further 25-30% will develop CRLM within two to three years of diagnosis[355]. Little is known of the impact of SES on the risk for CRLM and on outcomes of liver resection: a single

UK study demonstrated no association between social class and long term outcome following resection[356]. However, this study did not account for potential bias caused by patient selection for liver surgery. Patients with primary colorectal cancer often present symptomatically and are at risk of colonic obstruction, and population studies have shown that 60-80% of patients with primary colorectal cancer will be offered surgery[357]. However, the proportion of patients with CRLM who are offered surgery is far lower, at 10-20%[254,255]. Patients who develop CRLM must overcome a number of potential obstacles before undergoing liver surgery. They must survive surgery for primary colorectal cancer; they require long term surveillance imaging to detect metachronous lesions; they must be referred to a hepatobiliary unit; they must be medically fit for surgery, and their metastases technically resectable. Socioeconomic factors may influence a patient's ability to overcome these obstacles following surgery for primary colorectal cancer, which may potentially skew the population of patients submitted to surgery for CRLM in comparison with that of the population suffering primary colorectal cancer. A crude comparison of outcomes according to SES may therefore be less valid for CRLM as patients may be more stringently selected than those undergoing surgery for primary colorectal cancer.

The primary aim of this study was to compare levels of socioeconomic deprivation in patients undergoing liver resection for CRLM in a regional hepatopancreatobiliary (HPB) unit with those of the local population. A secondary aim was to determine if SES is associated with disease-free and overall survival.

10.3 Methods

A retrospective analysis was undertaken of a prospectively maintained database of all patients submitted to liver resection for CRLM between July 2005 and March 2012. Patient details, laboratory data and operative details were retrieved. Synchronous metastases were defined as those diagnosed prior to or within two months of primary surgery. All patients underwent tumour staging with computed tomography (CT) scan prior to liver surgery. Pre-operative magnetic resonance imaging (MRI) and positron emission tomography (PET) scans were performed at the discretion of the referring clinician. The physiological score was calculated using the POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) scoring system[297]. Post-operative surveillance CT scans were performed at six-monthly intervals for three years after liver resection and annually for another two years. All patients included in disease-free survival analysis underwent a minimum of one surveillance CT scan performed and the date of tumour recurrence was recorded.

Socioeconomic status was calculated using ACORN®[358], a commercially available geodemographic segmentation tool. This tool divides UK households into five categories in order of increasing deprivation, characterised as representing: wealthy achievers; the urban prosperous; the comfortably off; those of moderate means, and the hard pressed. The smallest unit of population for which information is available is based on postcode. Full postcodes allow accurate geographical breakdown because the median size of a residential postcode in the UK is 13 households, or 31 residents[358]. The deprivation category is based on data collected from multiple sources including

property value, type, occupancy and usage. Further information relating to residents is obtained and includes data on date of birth, ethnicity and receipt of social benefits, along with data on spending habits and lifestyle. Population density data are obtained from the National Census.

Patient survival curves were constructed using the Kaplan-Meier method and differences in survival were assessed using the log-rank method. Patients were excluded from survival analysis if they underwent planned non-curative resections or did not receive surveillance imaging. Comparisons between groups according to SES were performed using the chi-squared test or Mann-Whitney U-test, as appropriate. Potential associations between pre- and intra-operative factors, as well as histological outcome and tumour recurrence, were tested using univariate logistic regression or the chi-squared test, as appropriate. Variables in the univariate analysis for which differences achieved a P-value of <0.25 were included in the multivariate regression model[229]. Differences were considered to be significant at $P<0.05$. Univariate and multivariate analyses were carried out using the statistical package R 2.1.14[230].

Patient consent was not required for this study following confirmation from the South West Health Research Authority that under the harmonised Guidance Approval for Research Ethics Committees (REC), REC review is not required because patient data were collected during normal hospital care and was anonymised for research purposes.

10.4 Results

Data relating to 303 liver resections performed for CRLM over a period of seven years were analysed. Clinicopathological characteristics and operative details of the group are displayed in Table 10.1.

N=303		Median (Range)	Count (%)
Age		67 (33-90)	
Gender	Female		113 (37.3)
	Male		190 (62.7)
T stage of primary	0		3 (<1)
	1		7 (2.3)
	2		19 (6.3)
	3		174 (57.4)
	4		91 (30.0)
	Unavailable		9 (3.0)
N stage of primary	0		133 (43.9)
	1		101 (33.3)
	2		64 (21.1)
	Unavailable		5 (1.7)
Site of primary	Colonic		152 (50.2)
	Rectal		151 (49.8)
Timing	Synchronous		144 (47.5)
	Metachronous		159 (52.5)
Preoperative MRI	Yes		166 (54.8)
	No		137 (45.2)
Preoperative PET	Yes		208 (68.6)
	No		95 (31.4)
Preoperative liver directed chemotherapy	Yes		151 (49.8)
	No		152 (50.2)
Preoperative diabetes	Yes		28 (9.2)
	No		275 (90.8)
Body Mass Index (BMI)		27 (16-54)	
ASA Grade	1		24 (7.9)
	2		211 (69.6)
	3		68 (22.4)
Neutrophil lymphocyte ratio		2.58 (0.50-17.25)	
Preoperative albumin (g/d/L)		44 (26-52)	
POSSUM physiological score		16 (12-32)	
Operation	Right hemihepatectomy		129 (42.6)
	Extended right		13 (4.3)
	Left hemihepatectomy		35 (11.6)
	Extended left		3 (1.0)
	Left lateral sectorectomy		31 (10.2)
	Wedge resection		79 (26.1)
	Other		13 (4.3)
Radiofrequency ablation (RFA) included	Yes		19 (6.3)
	No		284 (93.7)
Wedge resection included	Yes		122 (40.3)
	No		181 (59.7)
Number of segments resected		4 (1-6)	
Repeat operation	Yes		33 (10.9)
	No		270 (89.1)
Curative resection	Yes		284 (93.7)
	No		19 (6.3)
Number of tumours		1 (1-10)	
Maximum diameter of tumours (mm)		35 (3-155)	
Resection margin	R0		232 (76.6)
	R1		71 (23.4)

Table 10.1 Preoperative and operative characteristics of 303 patients undergoing liver resection for CRLM.

The proportions of residents of Devon and Cornwall in the first and second (least deprived) (40.2%) and fourth and fifth categories (most deprived) (30.1%) SES categories differed from those of the UK (37.4% and 35.1% respectively) (P<0.001) (Table 10.2).

Deprivation category	UK Residents (%)	Residents of Devon and Cornwall (%)	Total number of patients undergoing liver resection (%)
1. Wealthy achievers (least deprived)	14 967 871 (24.8)	580 065 (34.6)	137 (46.4)
2. Urban prosperous	7 594 891 (12.6)	93 708 (5.6)	11 (3.7)
3. Comfortably off	16 656 466 (27.6)	497 182 (29.7)	93 (31.5)
4. Moderate means	8 449 324 (14.0)	271 357 (16.2)	31 (10.5)
5. Hard pressed (most deprived)	12 715 861 (21.1)	232 757 (13.9)	23 (7.8)
Total	60 384 413	1 676 069	295

Table 10.2 Distribution of population categorized by socioeconomic status in the UK, in Devon and Cornwall, and in those undergoing liver resections for CRLM.

Socioeconomic status was unclassified for eight patients. (Comparison between the proportion of residents of Devon and Cornwall and those undergoing liver resection: P<0.001)

Socioeconomic data were unavailable for eight patients undergoing liver resection, leaving 295 for analysis. Of these 295 patients submitted to liver resection for CRLM, the proportions of patients from the first and second (least deprived) categories (50.2%) and fourth and fifth (most deprived) categories (18.3%) of SES differed from the proportions in the local population (40.2% and 30.1% respectively) (P<0.001).

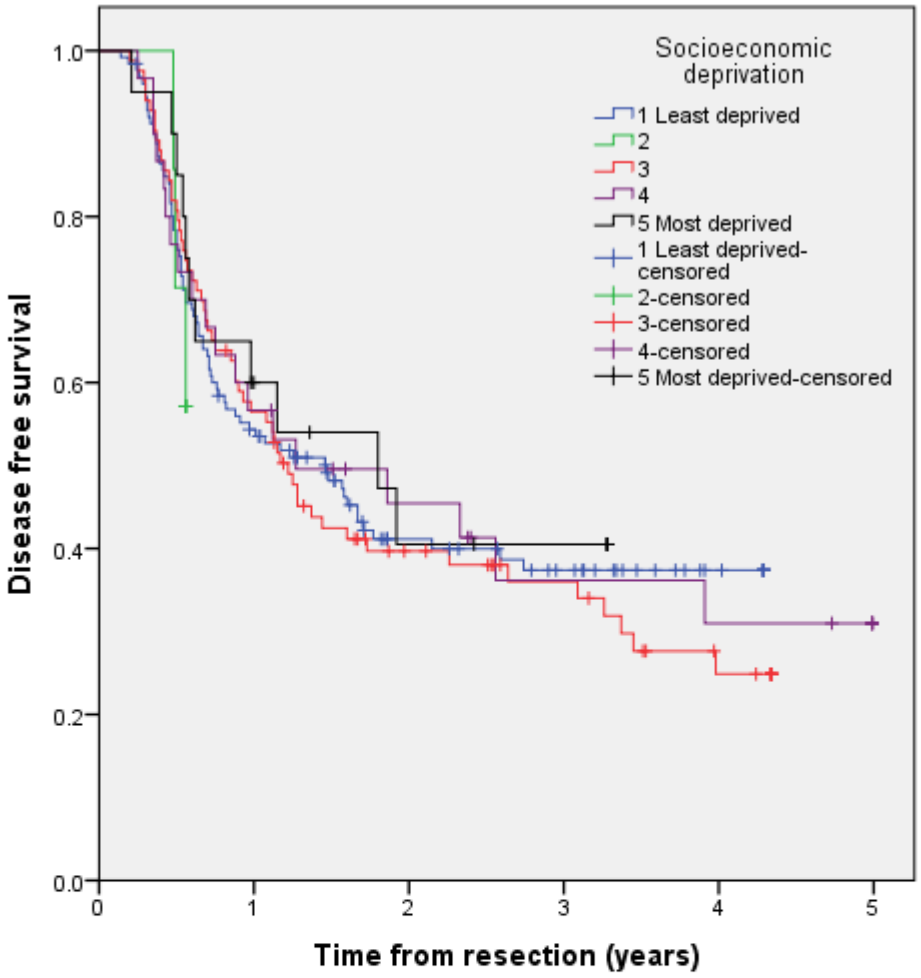
The clinicopathological and operative characteristics of the 148 least deprived (categories 1 and 2) and 54 most deprived patients (categories 4 and 5) are displayed in Table 10.3.

N=202		Least deprived categories (1 and 2) (n=148)		Most deprived categories (4 and 5) (n=54)		P-Value
		Median (Range)	Count (%)	Median (Range)	Count (%)	
Age		67 (34-88)		67 (33-90)		0.562
Gender	Female		56 (37.8)		23 (42.6)	0.625
	Male		92 (62.2)		31 (57.4)	
T stage of primary	0		2 (1.4)		0	0.060
	1		4 (2.7)		1 (1.9)	
	2		12 (8.1)		2 (3.7)	
	3		71 (48.0)		39 (72.2)	
	4		52 (35.1)		11 (20.4)	
	Unavailable		7 (4.7)		1 (1.9)	
N stage of primary	0		64 (43.2)		24 (44.4)	0.781
	1		50 (33.7)		16 (29.6)	
	2		30 (20.3)		13 (24.1)	
	Unavailable		4 (2.7)		1 (1.9)	
Site of primary	Colonic		77 (52.0)		29 (53.7)	0.874
	Rectal		71 (48.0)		25 (46.3)	
Timing	Synchronous		71 (48.0)		21 (38.9)	0.268
	Metachronous		77 (52.0)		33 (61.1)	
Preoperative MRI	Yes		83 (56.1)		29 (53.7)	0.873
	No		65 (43.9)		25 (46.3)	
Preoperative PET	Yes		111 (75.0)		25 (46.3)	<0.001
	No		37 (25.0)		29 (53.7)	
Preoperative liver directed chemotherapy	Yes		77 (52.0)		25 (46.3)	0.526
	No		71 (48.0)		29 (53.7)	
Preoperative diabetes	Yes		16 (10.8)		3 (5.6)	0.413
	No		132 (89.2)		51 (94.4)	
Body Mass Index		27 (17-39)		27 (19-54)		0.859
ASA Grade	1		16 (10.8)		1 (1.9)	0.030
	2		104 (70.3)		36 (66.7)	
	3		28 (18.9)		17 (31.5)	
Neutrophil lymphocyte ratio		2.38 (0.50-10.10)		2.85 (0.94-17.25)		0.161
Preoperative albumin (g/d/L)		44 (29-51)		43 (34-51)		0.102
POSSUM physiological score		16 (12-32)		17 (13-30)		0.720
Radiofrequency ablation (RFA) included	Yes		11 (7.4)		4 (7.4)	1.000
	No		137 (92.6)		50 (92.6)	
Wedge resection included	Yes		68 (45.9)		21 (38.9)	0.425
	No		80 (54.1)		33 (61.1)	
Number of segments resected		4 (1-6)		3 (1-6)		0.617
Repeat operation	Yes		15 (10.1)		4 (7.4)	0.786
	No		133 (89.9)		50 (92.6)	
Curative resection	Yes		136 (91.9)		53 (98.1)	0.191
	No		12 (8.1)		1 (1.9)	
Number of liver metastases		2 (1-10)		1 (1-8)		0.317
Maximum diameter of metastases (mm)		30 (3-120)		35 (5-120)		0.063
Resection margin	R0		115 (77.7)		44 (81.5)	0.698
	R1		33 (22.3)		10 (18.5)	

Table 10.3 Preoperative and operative characteristics of the 148 least (categories 1 and 2) and 54 most (categories 4 and 5) socioeconomically deprived patients undergoing liver resection for CRLM.

The use of PET scans was greater in the least deprived than in the most deprived group (75.0 vs. 46.3%) and the proportion of patients with American Society of Anesthesiologists (ASA) grade 1 status was higher in the least deprived (10.8%) compared to the most deprived (1.9%) group.

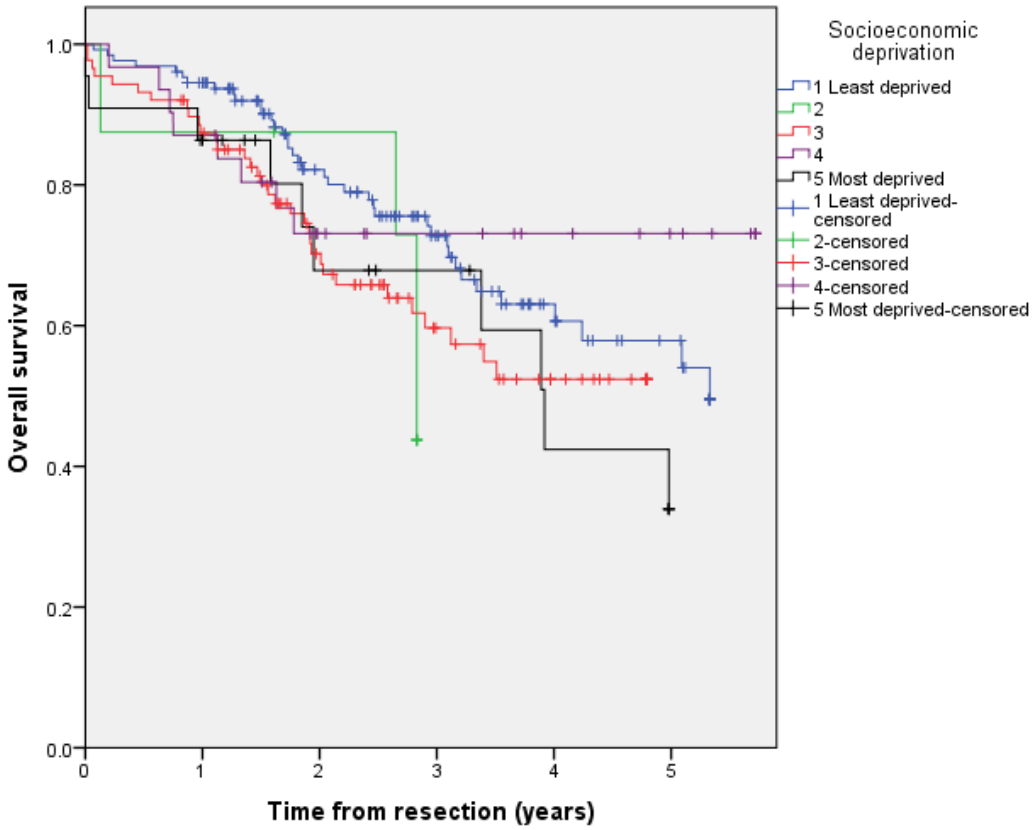
Data for 18 patients were excluded from the disease-free survival analysis because their resections were non-curative, or they did not complete a staged resection. Data for a further 11 patients were excluded because these patients died without undergoing surveillance imaging. This left a total of 266 patients for analysis. The median length of follow up was 1.07 years (range: 0.14-6.59) in the least deprived categories and 1.14 years (range: 0.21-7.36) in the most deprived categories (P=0.511). The median number of surveillance scans performed was three (range: 1-9) in both the least and most deprived categories (P=0.938). Tumour recurrence occurred in 163 patients; there was no difference in recurrence rate (77/133, 57.9% v 30/50, 60%) (P=0.867) or median time to recurrence between patients in the two least deprived (0.56 years; range 0.14-2.74 years) and two most deprived (0.61 years; range 0.21-3.91 years) (P=0.305). There was no difference among the disease-free survival curves of each category of SES (P=0.913) (Figure 10.1).



1 Least deprived					
Number at risk	126	66	35	26	13
Events		57	14	3	0
2					
Number at risk	7				
Events		3			
3					
Number at risk	83	46	25	18	9
Events		36	13	2	5
4					
Number at risk	30	17	11	7	6
Events		13	3	2	1
5 Most deprived					
Number at risk	20	11	6	5	
Events		8	3	0	

Figure 10.1 Kaplan–Meier disease-free survival curves of 266 patients undergoing planned curative liver resections who underwent surveillance imaging according to level of socioeconomic deprivation (Log rank P=0.913)

Among those patients who underwent planned curative resections and for whom socioeconomic data were available, including those in whom no surveillance imaging was performed (n=277), there were a total of 96 deaths during the study period (34.7%). There was no significant difference in mortality rate between patients in the two least deprived categories (42/136, 30.9%) and those in the two most deprived categories (18/53, 34.0%) (P=0.729). Twelve patients died within 90 days of surgery (4.3%), but there was no significant difference in 90-day mortality between patients in the two least deprived (4/136, 2.9%) and those in the two most deprived (3/53, 5.7%) categories (P=0.403). There was no difference in the overall survival curves across categories of SES (P=0.190) (Figure 10.2).



1 Least Deprived						
Number at risk	128	118	77	50	26	16
Events		7	13	8	6	2
2						
Number at risk	8	7	6			
Events		1	1			
3						
Number at risk	88	75	48	26	14	
Events		11	13	6	3	
4						
Number at risk	31	27	17	14	11	8
Events		4	4	0	0	0
5 Most deprived						
Number at risk	22	18	11	9	5	
Events		3	3	0	3	

Figure 10.2 Kaplan–Meier overall survival curves of 277 patients undergoing planned curative liver resections according to level of socioeconomic deprivation (Log rank P=0.190)

Multivariate analysis of factors potentially associated with tumour recurrence (Table 10.4) demonstrated no association between SES and tumour recurrence (P=0.700). Only the number of liver metastases (P=0.014) and maximum

tumour diameter (P=0.001) were associated with tumour recurrence. Each additional liver metastasis increased the risk of recurrence by a factor of 1.28, and each additional millimetre in tumour diameter had a small effect, increasing the risk of recurrence by a factor of 1.02.

N=266		Not recurred (n=103)		Recurred (n=163)		Univariate		Multivariate		
		Median (Range)	Count (%)	Median (Range)	Count (%)	P-Value	Odds Ratio (95% CI)	P-Value		Odds Ratio (95% CI)
Age[a]		65 (36-88)		67 (33-87)		0.872				
Gender	Male		67 (65.0)		105 (64.4)	0.863				
	Female		36 (35.0)		58 (35.6)					
Socioeconomic deprivation category	1 (least)		52 (50.5)		74 (45.4)	0.700				
	2		4 (3.9)		3 (1.8)					
	3		27 (26.2)		56 (34.4)					
	4		11 (10.7)		19 (11.7)					
	5 (most)		9 (8.7)		11 (6.7)					
T stage of primary	0,1 or 2		10 (9.7)		18 (11.0)	0.147[b]		0,1,2 vs. 3	0.504	0.79 (0.40-1.56)
	3		61 (59.2)		93 (57.1)			3 vs. 4	0.706	1.11 (0.68-1.80)
	4		29 (28.2)		47 (28.8)					
N stage of primary	0		50 (48.5)		67 (41.1)	0.828				
	1		34 (33.0)		53 (32.5)					
	2		18 (17.5)		40 (24.5)					
Site of primary colorectal tumour	Colon		55 (53.4)		75 (46.0)	0.389				
	Rectum		48 (46.6)		88 (54.0)					
Timing	Synchronous		46 (44.7)		78 (47.9)	0.584				
	Metachronous		57 (55.3)		85 (52.1)					
Preoperative chemotherapy			47 (45.6)		85 (52.1)	0.412				
Preoperative diabetes			7 (6.8)		15 (9.2)	0.523				
Body mass index (BMI)[a]		27 (19-54)		27 (16-50)		0.518				
ASA grade		2 (1-3)		2 (1-3)		0.566				
Preoperative albumin (g/dL)[a]		44 (34-50)		44 (26-52)		0.949				
POSSUM physiological score[a]		17 (12-32)		16 (12-32)		0.378				
Neutrophil:lymphocyte ratio (pre-op)[a]		2.4 (0.5-17.3)		2.6 (0.7-9.1)		0.211[b]	1.09 (0.95-1.26)	0.079		1.09 (0.94-1.28)

Table 10.4 Univariate and multivariate analysis of factors associated with tumour recurrence following liver resection for CRLM in 266 patients.

Table 10.4 continued.

N=266	Not recurred (n=103)		Recurred (n=163)		Univariate		Multivariate	
	Median (Range)	Count (%)	Median (Range)	Count (%)	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)
Preoperative MRI		59 (57.3)		87 (53.4)	0.640			
Preoperative PET		68 (66.0)		110 (67.5)	0.930			
Wedge resection included		31 (30.1)		67 (41.1)	0.117[b]		0.062	1.70 (0.98-2.94)
Radiofrequency ablation (RFA)		6 (5.8)		10 (6.1)	0.959			
Number of segments resected[a]	4 (1-6)		4 (1-6)		0.222[b]	1.10 (0.94-1.28)	0.120	1.00 (0.94-1.07)
Repeat operation		11 (10.7)		18 (11.0)	0.105[b]		0.824	1.04 (0.39-2.77)
Number of tumours[a]	1 (1-7)		2 (1-10)		0.007[b]	1.29 (1.07-1.55)	0.014	1.28 (1.06-1.56)
Diameter of largest tumour (mm)[a]	28 (3-155)		35 (6-150)		0.002[b]	1.02 (1.01-1.03)	0.001	1.0 (1.00-1.04)
Resection margin <1mm (R1)		18 (17.5)		45 (21.2)	0.212[b]		0.372	1.03 (0.94-1.07)

In univariate analysis, continuous variables[a] tested with logistic regression. Categorical variables tested with chi square test. [b]Significant at the level of <0.25 for univariate analysis and tested in multivariate analysis.

10.5 Discussion

The principal finding of this study is that the SES of patients undergoing liver resection for CRLM is not representative of that of the local population because the proportion of patients from the least deprived categories is higher than expected and that of patients from the most deprived categories is lower than expected. Amongst patients undergoing liver resection for CRLM, the degree of socioeconomic deprivation had no effect on tumour recurrence after resection.

The finding that people from the least deprived categories of SES account for a higher proportion of patients undergoing liver surgery for CRLM than they do in the local population is significant and in keeping with the present authors' clinical observations. The comparison is subject to bias as the incidence of colorectal cancer is influenced by SES and the disease is more common in populations with the greater levels of deprivation[132]. This would tend therefore to increase the differences observed in the proportions of the different population categories submitted to liver surgery in comparison with those within the local population because CRLM would be expected to occur more commonly amongst patients of lower SES. There are many potential reasons why patients with the least deprivation are more likely to undergo surgery for CRLM, despite being at lower risk for development of colorectal cancer. Patients with higher levels of deprivation are more likely to suffer post-operative complications and death following primary colorectal cancer surgery[359] and are likely to have more or more severe comorbidities that render them unfit for further surgery. Socioeconomic status is associated with educational attainment[360], and patients with greater deprivation may be less aware of the potential benefits of treatment for metastatic disease. This may affect patients'

willingness to engage with long-term surveillance to detect metachronous disease and to seek referral to an HPB unit. There is also an element of discretion by clinical practitioners in many stages of the patient pathway prior to surgery for CRLM, which may be influenced by perceptions of degree of socioeconomic deprivation.

Interestingly, there was a large disparity in the use of staging PET scans, which were performed in 74.5% of patients from the least deprived groups compared with only 30.4% of patients from the most deprived. This may be partly explained by the higher incidence of T4 primary tumours amongst the least deprived patients, which is one of the indications for PET scans in national guidelines[122], but is not otherwise explicable by the other measures of disease burden used in this study.

There was no difference in objective measures of health between patients in the highest and lowest categories of SES as shown by the presence of preoperative diabetes, physiological score or body mass index. This may reflect the greater selection of patients from more deprived groups, in whom the rate of these markers of poor health might be expected to be higher. There was, however, a small difference in subjective measures of health as determined by ASA grade.

To categorize SES, this study used the ACORN® system, which has been used in a number of epidemiological studies[361–364]. This system has advantages in that economic data are drawn from a wide range of sources in addition to property values. Other studies addressing the influence of SES on healthcare outcomes have used the Income Domain of the Index of Multiple Deprivation (IMD) score [365] and the Townsend index [366]. These systems have been used

simultaneously in previous studies[367,368] and neither method has been shown to be superior. Moreover, the difficulties of analysing and interpreting socioeconomic data have been described[369]. However, the systems allow for the valid and simultaneous comparison of different populations in contexts in which potential bias and inaccuracy will affect the populations under study equally.

In a manner reflecting the findings of previous work[356] degree of socioeconomic deprivation was not shown to be associated with either 90-day mortality or disease recurrence. The most likely explanation for this to be derived from the present data is not that SES does not affect these outcomes, but that greater selection occurs amongst patients of lower SES to favour patients who are likely to have better outcomes.

The difference in the rates of liver resection for CRLM according to SES may reflect selection based on objective health measures. However, further study however is required to confirm this and to ensure equity of access to specialised hepatobiliary services within a publicly funded healthcare system. Similar differences may be found in other countries, especially those with systems of predominantly private health insurance, and selection of patients for surgery based on SES may influence the comparison of outcomes between countries.

Further research is needed to understand the reasons why patients from more deprived groups are less likely to be referred for liver resection. Liver surgeons should ensure that other specialists and general practitioners understand the role of liver resection for colorectal liver metastases to avoid patients being

denied the possibility of potential curative surgery.

Chapter 11 : Thesis Summary and Conclusion

This thesis follows the pathway of patients from referral to a regional hepatopancreaticobiliary unit through to postoperative surveillance. Over a seven-year period 504 liver resections were performed.

The key findings of this thesis are as follows;

1. Approximately 10% of patients proceeding to surgery following MDT discussion have inaccurate diagnoses and 5% are understaged despite an increase in the number of imaging modalities used.
2. In the staging of patients with CRLM, the use of MRI in addition to CT showed no association with lower rates of post-operative intra-hepatic tumour recurrence or disease-free survival.
3. There was no association between tumour doubling time prior to surgery and post-operative survival.
4. Disease-free survival is determined by tumour behaviour during treatment and not by change in size after completion of chemotherapy.
5. The major complication rate was 18.7% and was significantly associated with age, male gender, insulin-dependent diabetes, hypoalbuminaemia, synchronous bowel procedures, the extent of resection and requirement for blood transfusion.
6. Post-operative serum lactate predicted the 90-day mortality rate (28% when post-operative lactate ≥6mmol/L compared to 0.7% when lactate ≤2mmol/L).

7. The 90-day mortality rate was 2.7% in patients without post-hepatectomy liver failure or renal dysfunction, 20% in patients with single organ dysfunction and 45% in patients with both.
8. Recurrence rates following liver resection for CRLM were lower in patients when a fibrous tumour pseudocapsule was present.
9. Liver resection for CRLM was performed less frequently among the most socioeconomically deprived population. However, socioeconomic deprivation was not associated with tumour recurrence.

The beginning of the patient journey begins with discussion of patients at a regional multidisciplinary team meeting. Over a six-year period there had been a 50% increase in the number of imaging modalities used during the assessment of patients put forward for liver resection. This increase in imaging modalities was due to the increased use of MRI and PET scans but this did not correlate with a reduction in the rate of non-resection or rate of discrepant diagnosis. Around 5% of patients still undergo unnecessary surgery for benign lesions.

Overall 10% of patients proceeding to surgery are subsequently shown to have inaccurate diagnoses. The highest rate of discrepant diagnoses occurred in the group of patients with focal liver lesions but no history of chronic liver disease or primary cancer (38%). In this group multimodality imaging should be considered but care should be taken to assess this imaging in the context of the clinical history.

Interestingly, whilst investigating the impact of social deprivation in patients undergoing liver resection for CRLM it was noted that the use of PET scans was significantly greater in patients from the least deprived group (74.5%) compared to those patients from the most deprived (30.4%). This may be explained by either selection bias or the higher incidence of more advanced primary tumours in the least deprived group which is one of the indications for PET in national guidelines, although this had no impact on tumour recurrence.

MRI scans with diffusion-weighted imaging have only been available within the region since 2011 and this may explain their increased use during the study period. Not only did the increased use of MRI lead to no improvement in the assessment of liver lesions in general, it was also demonstrated that in those patients with CRLM there were similar rates of accuracy in identifying the number of liver metastases in patients staged with CT and those with additional MRI. Moreover, MRI tended to overstage patients in terms of tumour number with the potential for patients to be denied liver surgery if lesions are falsely identified. The use of MRI was also associated with a delay in the time to surgery which may result in tumour progression prior to resection which many patients would find increasingly stressful.

Significantly, the additional use of MRI conveyed no benefit in terms of tumour recurrence or disease-free survival in patients undergoing resection for CRLM when intraoperative ultrasound is used. The role of MRI in national guidelines is not clearly defined in this context but the findings of this study suggest that the use of MRI should not be mandatory in the assessment in patients with both CRLM and other potentially resectable liver lesions as the cost and delay associated with the scan outweigh the potential small benefit in terms of

improved sensitivity. This is however dependent on the use of IOUS which can be performed at low cost and not impact on time to surgery.

Although scoring systems have been developed for the prediction of outcome following liver resection[167,188,316,370,371] this thesis has demonstrated several novel findings as well as supporting those of previous studies. There was a 90-day mortality rate of 4.6% in this series and of the 21 postoperative deaths 11 were due to PHLF. The “50-50” criteria[186] has previously been advocated as a predictor of PHLF and mortality but in this series, it had no value as a predictor of PHLF or mortality following liver resection. However, the ISGLS definition of PHLF defined as a post-operatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions, characterized by an increase in INR and hyperbilirubinaemia on or after postoperative day five[187], was shown to be an independent predictor of 90-day mortality with a PPV of 23% and a NPV of 97% in keeping with a previous study[333]. The presence of PHLF on postoperative day five increased the risk of mortality by a factor of 4.5.

Postoperative renal dysfunction occurred in between six and seven percent of patients and was also an independent predictor of 90-day mortality following liver resection, increasing the risk by a factor of 3.6. A novel finding is that the PPV of PHLF as a predictor of 90-day mortality is significantly higher when it occurs alongside renal failure with a PPV of 45% and NPV of 97%. Therefore, although the ISGLS definition has been validated as a predictor of mortality, the development of renal dysfunction in this context is the single most important predictive factor and we suggest that PHLF and postoperative renal dysfunction

should be used in conjunction when predicting 90-day mortality following liver resection.

Preoperative factors shown to be associated with 90-day mortality included older age, male gender, preoperative hypoalbuminaemia and diabetes mellitus in accordance with previous findings[136,337]. The presence of diabetes mellitus was also an independent risk factor for major complications after liver surgery which is again in keeping with previous studies[60,163,164]. However, another novel finding is that insulin dependence is the major risk factor rather than diabetes itself.

Along with increased BMI, diabetes was associated with hepatic steatosis, although steatosis itself did not increase the risk of major complications after surgery. Postoperative renal dysfunction was twice as common in patients with insulin dependent diabetes compared to those not requiring insulin therapy, which itself was a predictor of 90-day mortality. The major risk factors in this series related to the surgery itself. Extent of resection and requirement for blood transfusion were independently associated with postoperative complications as previously demonstrated[136]. In contrast with a previous systematic review which suggested it is safe to perform synchronous bowel resections[312] the findings of this study suggest that the risk of developing a major complication after a synchronous bowel resection was almost six times higher than when liver resection was performed alone.

A key finding of this thesis is that initial serum lactate is a predictor of renal and hepatic dysfunction as well as 90-day mortality. The incidence of both renal dysfunction and mortality in patients with initial lactate concentrations greater

than 6mmol/L were 28% compared to 0.7% and 2.2% in patients with normal lactate concentrations <2mmol/L. Operative factors associated with a raised initial lactate concentration included extent of resection, blood loss and requirement for blood transfusion. There was also an association with diabetes mellitus. These findings are of value in clinical practice as those patients with initial lactate concentrations <2mmol/L are at low risk of organ dysfunction and mortality and therefore may not need post-operative critical care which may have significant financial and operational benefits for healthcare systems.

In patients undergoing liver resection for colorectal liver metastases it was clear that the socioeconomic status of patients is not representative of that of the local population with more patients form the least deprived categories and fewer from the most deprived categories undergoing resection. There were no significant differences in the presence of diabetes, BMI or POSSUM physiological score between groups which would normally be expected in the general population, suggesting greater selection amongst the most deprived groups in whom these markers of poor health are more common. Importantly there was no association between the degree of socioeconomic deprivation and either 90-day mortality or disease recurrence which once again suggests that patient selection occurs to favour patients who are likely to have improved outcomes.

In contrast to other solid tumours including colorectal lung metastases the rate of growth of untreated CRLM prior to liver resection had no impact on tumour recurrence or disease-free survival. In this context, the rate of growth of CRLM should therefore not be regarded as a predictor of poor outcome in terms of

recurrence and disease-free survival when patients are discussed at the MDT pre- or post-operatively.

Where patients do receive liver-directed chemotherapy prior to liver resection for CRLM this study has demonstrated that in many patients the treatment effect is transient, and tumours continue to grow in the period between finishing chemotherapy and undergoing liver resection. However, it is their initial response to treatment that predicts disease-free survival despite rapid rebound growth in the interval before surgery, which has no association with disease-free survival. This is the first study to address this rebound phenomenon and may be useful when addressing the timing of surgery. Patients are often concerned about the potential delay in proceeding to surgery because of the risk of further tumour growth. The results of this study can be used to counsel such patients both pre- and postoperatively where there may have been considerable increase in size of tumours at the time of resection.

Aside from continuing in surveillance programmes, the final part of the patient journey occurs when the histopathology report of the resected specimen is discussed at the MDT. Both the number of metastases and maximum diameter of metastases are measured in the histology report. Although these are important prognostic indicators this information is often available from preoperative imaging and is of little additional benefit. A positive resection margin appeared to be an important prognostic factor in one of the multivariate analyses performed whilst investigating the presence of pseudocapsules. However, this analysis included cases of recurrence at the cut surface of the liver and when these patients were excluded from analysis no association between resection margin status and tumour recurrence was demonstrated.

The finding that in patients undergoing resection for synchronous CRLM the presence of a fibrous pseudocapsule may be a predictor of lower early recurrence is, however novel and warrants further investigation. This may have clinical significance for patients with synchronous CRLM who are found to lack the presence of a pseudocapsule and further treatment or surveillance may be tailored for this group.

11.1 Overall conclusion

This work can aid clinicians in the decision making and patient selection for liver resection. The findings may be used to effectively counsel patients preoperatively regarding the risks and benefits of liver resection. Furthermore, some of the findings may have a real impact upon healthcare provision in this patient group. In a public health service with ever increasing demand and costs careful patient selection is essential.

Although the studies in this thesis are historical cohort studies (level 4 evidence) they have allowed us to ask novel questions regarding the pathway of patients undergoing liver resection and have revealed questions that can be further examined in other ways. Clinicians should use this evidence to further assess and analyse current local and national practices to ultimately improve patient care. It is recommended that clinicians could;

1. Consider multimodality imaging in the diagnosis of hepatic tumours, but care should be taken to assess this imaging in the context of the clinical history.

2. Further evaluate the role of preoperative MRI in the preoperative staging of colorectal liver metastases as new technology and protocols evolve and assess the impact on patient outcomes rather than simply the ability to detect lesions.
3. Not use rate of growth of colorectal liver metastases as a predictor of poor outcome in terms of tumour recurrence and disease-free survival when patients are discussed at MDT pre- or post-operatively until this has been further assessed.
4. Use the evidence that preoperative patient factors such as older age, male gender, preoperative hypoalbuminaemia and diabetes mellitus are associated with morbidity to counsel patients regarding their individual risks associated with liver resection prior to embarking on surgery.
5. Measure the initial lactate postoperatively to guide decision making regarding the level of postoperative care required such as ITU or HDU.
6. Use the ISGLS definition of PHLF and in combination with renal dysfunction to make assessments of patients' clinical progress to guide the level of postoperative care required and to better inform patients and their relatives of clinical progress.
7. Encourage routine histopatholoical reporting of the presence of pseudocapsules surrounding colorectal liver metastases to enable further assessment of this feature and its association with tumour recurrence which may guide postoperative surveillance and treatment.

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Research Article

The Preoperative Assessment of Hepatic Tumours: Evaluation of UK Regional Multidisciplinary Team Performance

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Introduction. In the UK, patients where liver resection is contemplated are discussed at hepatobiliary multidisciplinary team (MDT) meetings. The aim was to assess MDT performance by identification of patients where radiological and pathological diagnoses differed. *Materials and Methods*. A retrospective review of a prospectively maintained database of all cases undergoing liver resection from March 2006 to January 2012 was performed. The presumed diagnosis as a result of radiological investigation and MDT discussion is recorded at the time of surgery. Imaging was reviewed by specialist gastrointestinal radiologists, and resultswere agreedon by consensus. *Results*. Four hundred and thirty-eight patients were studied. There was a significant increase in the use of preoperative imaging modalities ($P \leq 0.01$) but no change in the rate of discrepant diagnosis over time. Forty-two individuals were identified whose final histological diagnosis was different to that following MDT discussion (9.6%). These included 30% of patients diagnosed preoperatively with hepatocellular carcinoma and 25% with cholangiocarcinoma of a major duct. *Discussion*. MDT assessment of patients preoperatively is accurate in terms of diagnosis. The highest rate of discrepancies occurred in patients with focal lesions without chronic liver disease or primary cancer, where hepatocellular carcinoma was overdiagnosed and peripheral cholangiocarcinoma underdiagnosed, where particular care should be taken. Additional care should be taken in these groups and preoperative multimodality imaging considered.

1. Introduction

Cancer care in the UK has undergone a major change in recent years with the centralisation of care in a network of cancer centres [1]. This has led to the establishment of regional hepatopancreaticobiliary (HPB) units where patients in whom liver resection is contemplated are discussed at a multidisciplinary team (MDT) meeting in the presence of radiologists, oncologists, surgeons, and physicians. This is intended to provide greater clinical input into the diagnosis of the wide spectrum of disease processes for which liver resection is appropriate [2]. During the same period increasing awareness of the complimentary role of different imaging modalities in diagnosing liver disease [3–5] has led to many patients having multiple investigations prior to surgery. Although the accuracy of single imaging modalities including ultrasound [3, 6, 7], computerised tomography (CT) [3, 7, 8], magnetic resonance imaging (MRI) [3, 7, 9], and positron emission tomography (PET) [3, 8] scans in assessing hepatic malignancies has been well described, the performance of MDT review of multiple preoperative imaging techniques with input from clinicians in the diagnosis of malignancy and planning of treatment has not been described.

The Peninsula HPB unit was founded in July 2005 to serve the Devon and Cornwall region of England (population 1.7 million). Imaging from referring hospitals is imported and discussed in a weekly MDT meeting, and treatment recommendations are made and recorded. After resection histology of the excised sample is also discussed at the MDT

meeting. Despite MDT assessment, we have experienced cases either where the histological diagnosis has differed from the presumed preoperative diagnosis or where the available imaging does not allow a certain diagnosis to be made. In this situation a list of differential diagnoses is made from which treatment is recommended. Furthermore, despite advanced imaging techniques, some patients undergo surgery without proceeding to resection due to unexpected operative findings. The primary aim of this study was to identify patients where the diagnosis determined by the MDT differed from the final histological diagnosis. A secondary aim was to identify recurring areas of confusion to guide future MDT assessment and to determine if the rate of inaccurate diagnosis of liver tumours and assessments of resectability of liver lesions has changed over time.

2. Materials and Methods

The Peninsula HPB unit has maintained a prospective database since the inception of the unit where the outcome of MDT discussion is recorded prior to surgery. A review of all patients undergoing surgery from March 2006 to January 2012 was performed. Details of preoperative diagnosis, imaging modalities performed, operative findings, and final histology were retrieved. Patients were identified where the MDT was unable to make a definitive diagnosis leading to differential options. All imaging was re-reviewed by a specialist gastrointestinal radiologist and results agreed by consensus. For comparison of utilisation of imaging modalities, the group was split into two halves consisting of 219 patients each. The dataset was also divided to compare the earlier with later experience. Statistical analysis was performed using a chisquare test or Mann-Whitney U test, and a P value of <0.05 was considered statistically significant. Analyses were performed using SPSS version 20 (IBM, New York, USA).

3. Results

3.1. Patient Population. Four hundred and thirty-eight patients were identified including 248 males and 190 females with median age 65 years (range 21–90). The indications for surgery are shown in Table 1. Four hundred and seventeen patients underwent liver resection (95%), and 21 patients (5%) underwent surgery without resection. Details of the group not proceeding to resection are shown in Table 2.

3.2. Imaging Performed. In total 969 imaging investigations (excluding repeat images of the same modality) were performed for the 438 patients including CT, MRI, PET, US, and ERCP. Only five patients did not have a CT scan. The number of MRI scans undertaken increased from 96 in the first half of the study (219 patients) to 131 in the second the second ($P = 0.001$). Similarly the number of PET scans undertaken increased from 85 to 115 ($P = 0.005$). In a minority of patients ERCP or Octreotide scans were performed where indicated.

The total number of investigations performed increased significantly during the study period from 442 in the first half to 525 in the second. Similarly, the median number of scans performed per patient increased from two (1–4) to three (1–4) ($P < 0.001$).

3.3. Correlation of MDT Assessment with Operative Findings. A decision not to resect was made in 21 patients (4.8%) either because of peritoneal disease, tumour progression or because no malignant lesion could be identified (Table 2).

There was no change in the rate of nonresection over time (10/219 versus 11/219). MDT assessment of operability was most accurate for CRM where only 7/270 patients (2.6%) were not resected and least accurate for patients with hilar cholangiocarcinomas where 4/23 patients were not resected ($P < 0.001$).

3.4. Correlation of MDT Diagnosis with Final Pathology. Of the 438 patients operated on in this period 42 individuals were identified whose final histological diagnosis was different to the outcome of the MDT discussion (9.6%) (Table 1). There was no change in the rate of discrepant diagnosis over time (23/219 versus 19/219) (Table 3). The median number of lesions per patient was one in both the first (range 0–9) and second (range 0–20) halves of the series ($P = 0.057$). Similarly there was no difference in maximum tumour size with a median of 35 mm (range 6–210) in the first half and 35 mm (range 3–230) in the second ($P = 0.936$). The median number of imaging modalities used was three in patients with discrepant diagnoses compared to two in those with correct diagnoses ($P = 0.003$). The only difference occurred in the use of MRI where 31/42 (73.8%) patients with discrepant diagnoses had additional MRI compared to 196/396 (49.5%) patients where the diagnosis was correct ($P = 0.003$). In total twenty-two patients (5%) underwent hepatic resection for what proved to be benign disease having been diagnosed with malignancy preoperatively. The difficult areas of MDT assessment fell into the following categories.

3.5. Hepatocellular Cancer. Thirteen of 44 patients diagnosed as having hepatoma at MDT and proceeding to resection had different histological diagnoses after surgery, of which three were benign. There was no significant difference in the rate of discrepant diagnosis in those with and without a history of chronic liver disease (CLD) (6/19 versus 7/25) (Table 4). In six patients with CLD the final histology revealed a mixed type of tumour with features of both hepatoma and cholangiocarcinoma. For the purposes of this study these have been classed as correct diagnoses.

3.6. Cholangiocarcinoma of Major Hepatic Duct. All patients with suspected cholangiocarcinoma of a major hepatic duct underwent cholangiography (percutaneous, endoscopic, or MR) in addition to cross-sectional imaging. Seven of 28 patients diagnosed with cholangiocarcinoma at MDT had a different histological diagnosis after resection (Table 3). There was no significant difference in the rate of incorrect diagnosis in those who presented with obstructive jaundice (3/19) and those without (4/9). Of those patients diagnosed with cholangiocarcinoma without obstructive jaundice, the diagnosis was confirmed in five patients on final histology.

Table 1: MDT indications for resection and number with discrepant histological diagnoses.

Primary MDT diagnosis	Number (%)		Median age (range)		Male/female	Discrepant diagnosis (%)	
Colorectal liver metastases (CRM)	279	(64)	67	(33–90)	176/103	10	(3.6)
Hepatoma	44	(10)	63	(33–84)	31/13	13	(30)
Hilar cholangiocarcinoma	28	(7)	67	(32–77)	14/14	7	(25)
Other metastases	24	(5)	62	(32–76)	8/16	1	(4)
Gall bladder carcinoma	20	(5)	61	(41–82)	5/15	1	(5)
Neuroendocrine tumour (NET)	11	(3)	51	(41–77)	8/3	0	—
Metastasis of unknown origin	6	(1)	63	(43–73)	4/2	5	(83)
Biliary cystadenoma	6	(1)	34	(21–43)	0/6	0	—
Focal nodular hyperplasia (FNH)	5	(1)	34	(30–38)	0/5	0	—
Hepatocellular adenoma	4	(<1)	31	(30–39)	0/4	0	—
Benign cyst	3	(<1)	52	(47–65)	0/3	1	(33)
Breast metastases	3	(<1)	67	(45–78)	0/3	3	(100)
Peripheral cholangiocarcinoma	3	(<1)	70	—	2/1	1	(33)
Primary sarcoma	1	(<1)	71	—	0/1	0	—
Haemangioma	1	(<1)	33	—	0/1	0	—
Total	438		65	(21–90)	248/190	42	(9.8)

Table 2: Reasons for nonresection.

Final diagnosis	Number (%)		Peritoneal disease	Disease progression	No/benign disease
Colorectal metastases (CRM)	7/270	(2.6)	4	3	0
Hepatoma	2/33	(6)	0	2	0
Hilar cholangiocarcinoma	4/23	(17)	0	4	0
Gall bladder carcinoma (GBC)	2/19	(11)	2	0	0
Other metastases	3/30	(10)	1	2	0
Neuroendocrine tumour (NET)	1/13	(8)	0	1	0
Haemangioma	1/9	(11)	0	0	1
Normal liver	1	—	0	0	1
Total	21	(4.8)	7	12	2

3.7. Colorectal Metastases. All patients diagnosed with CRM had a history of colorectal cancer, but 10 (3.6%) had different histological diagnoses after resection (Table 3), of which six were benign. Six of these were metachronous lesions and four were synchronous with their colorectal cancer diagnosis ($P = 0.539$).

3.8. Solid Liver Lesions with No History of Chronic Liver Disease or Primary Malignancy. Thirty-four patients underwent resection of peripheral liver lesions (including hepatomas) with no history of CLD or primary malignancy of whom 13 had discrepant diagnoses (Table 4).

Peripheral cholangiocarcinoma was rarely diagnosed correctly preoperatively. Of eleven patients with a diagnosis of peripheral cholangiocarcinoma at histology, only two had been diagnosed correctly preoperatively, both by percutaneous biopsy. The remainder were inaccurately diagnosed as hepatomas or metastases (Table 3).

3.9. Adenoma/FNH/Hepatocellular Carcinoma. A group of 10, predominantly young, female patients (median age 33, range 33–63) was identified in whom the MDT differential list included FNH, adenoma, or hepatocellular carcinoma. After resection all patients had a histological diagnosis that was included in the alternatives made at MDT. In five patients histology revealed hepatic adenoma, four revealed FNH, and one a hepatoma.

4. Discussion

This study reveals a number of important features of the MDT assessment of patients with focal liver lesions during the six-year development of a regional HPB unit. Firstly there has been a 50% increase in the number of imaging modalities used in the assessment of these patients over a short time interval. This has been caused by an increased utilisation of PET scans and MRI due to an increased awareness of their role and improved access. Although PET scans have poor sensitivity for detecting multiple liver lesions, they are valuable in the preoperative assessment of patients with hepatic CRM to exclude extrahepatic disease [10, 11]. MRI scans with diffusion-weighted imaging have been shown to

Table 3: Discrepant diagnoses in 42 patients.

MDT diagnosis	Total discrepant	Histological diagnosis																
		Angiomyolipoma* (1)	Benign cyst* (4)	Benign fibrosis* (3)	Bile duct papilloma* (1)	Breast metastasis (3)	Peripheral cholangiocarcinoma (11)	CRM (270)	FNH* (6)	Focal fat* (2)	Haemangioma* (9)	Hepatoma (34)	NET (13)	No lesion* (2)	Sarcoma (4)	Chronic inflammation* (1)	Ovarian metastasis (5)	Xanthogranulomatous cholecystitis* (1)
Hepatoma (44)	**13**	1	—	—	—	—	5	1	—	1	2	—	2	—	—	1	—	—
Colorectal metastases (CRM) (279)	**10**	—	—	—	—	2	1	—	—	—	4	1	—	2	—	—	—	—
Hilar cholangiocarcinoma (31)	7	—	2	3	1	1	—	—	—	—	—	—	—	—	—	—	—	—
Metastases of unknown origin (6)	5	—	—	—	—	—	3	—	—	—	1	—	—	—	1	—	—	—
Breast metastases (3)	3	—	—	—	—	—	—	—	—	1	1	1	—	—	—	—	—	—
Peripheral cholangiocarcinoma (3)	1	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—
Anal metastases (7)	1	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—
Benign cyst (3)	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—
Gall bladder carcinoma (20)	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Total	**42**	**1**	**2**	**3**	**1**	**3**	**9**	**1**	**1**	**2**	**8**	**3**	**2**	**2**	**1**	**1**	**1**	**1**

Total number of each diagnosis in the series (438) shown in brackets.

All MDT diagnoses of neuroendocrine tumours (NET) (11), focal nodular hyperplasia (FNH) (5), biliary cystadenoma (6), primary sarcoma (1), and haemangioma (1) were confirmed on histology.

*Benign pathology.

Table 4: MDT and histological diagnoses of 34 patients with peripheral liver lesions and no history of CLD or malignancy.

MDT diagnosis	Histology								
	Hepatoma	Peripheral cholangio-carcinoma	Haem-angioma	Neuroendocrine tumour	Metastasis of unknown origin (MUO)	Hepatic sarcoma	Focal nodular hyperplasia	Fat	Total
Hepatoma	18	4	1	1	—	—	—	1	25
Metastases of unknown origin	—	3	1	—	1	1	—	—	6
Peripheral cholangiocarcinoma	—	2	—	—	—	—	1	—	3
Total	18	9	2	1	1	1	1	1	34

have greater sensitivity than CT in the detection of CRM [8, 12], hepatoma [13], and metastatic NET [14], although these scans have only been available to this department since 2011. The policy of this unit is not to biopsy potentially resectable liver lesions due to the potential risk of tumour seeding [15, 16].

In this series 21 patients (5%) did not undergo surgical resection, and the rate of non-resection did not change significantly over time. The rate of non-resection of liver lesions following assessment has been described previously with reported rates of 3–12% [17, 18]. The commonest cause of non-resection in our series was disease progression. The time interval between imaging and surgery may have a major impact on this outcome, limiting the value of modern imaging. Peritoneal disease was noted in seven of the unresected patients, which is not readily identified by any imaging modality [19].

The highest rate of discrepancies in our series occurred in the group of patients with focal liver lesions without a history of chronic liver disease or primary cancer. This finding emphasises the importance of assessing imaging in the context of the clinical history (13/34). Two observations arise from this group of significance in clinical practice. Firstly the majority of patients (5/6) diagnosed with metastases of unknown origin (MUO) have defined histology after resection, of which the most common is peripheral cholangiocarcinoma. These lesions typically have hypovascular appearances on imaging with ring-like enhancement [20] and can easily be misdiagnosed as colorectal or breast metastases [21]. Recently published guidelines for the management of MUO recommend a range of chemotherapy regimens [22], none of which have been shown to be of benefit in the treatment of cholangiocarcinoma, whereas surgical resection of peripheral cholangiocarcinoma is of proven benefit [23] but is rarely appropriate in the treatment of MUO. Similarly 4/25 patients diagnosed as having hepatoma in this setting are ultimately shown to have peripheral cholangiocarcinoma. Peripheral cholangiocarcinoma is less common than hepatocellular carcinoma [24] which may lead to a low index of suspicion in MDT diagnosis.

In patients with a history of CLD and focal liver lesions, there remains a high rate of patients found not to have hepatoma after excision (7/19). These include neuroendocrine metastases which are hypervascular lesions having similar radiological appearances to hepatoma. This has implications for this patient group where treatment is often recommended without a histological diagnosis.

The commonest indication for liver resection in our series has been CRM, and the rate of discrepant diagnoses for this group is low (3.6%). The most common alternative diagnosis after resection in this group was haemangioma. The radiological characteristics of this group have been described elsewhere [25] and can be difficult to distinguish from metastases. Interestingly two patients in this group were found to have breast cancer metastases after primary breast surgery two and ten years previously. Breast metastases can have similar radiological features to CRM and can occur many years after the primary diagnosis. A further breast metastasis occurred as an obstructing lesion of the left hepatic duct sixteen years after primary surgery and was diagnosed as a hilar cholangiocarcinoma.

The high rate of discrepant diagnoses in patients with major duct cholangiocarcinoma has been shown previously [26–28]. These lesions are usually sclerosing adenocarcinomas causing biliary obstruction and are often not visible as a mass lesion [20]. In this situation the presence of the lesion is inferred by the radiological finding of ductal dilation along with clinical features of obstruction. The most common alternative diagnosis in this series was ductal fibrosis. This condition may be a manifestation of an autoimmune process and can have similar radiological features to cholangiocarcinoma [29]. Peribiliary cysts can often be diagnosed preoperatively by the presence of multiple cysts but can also mimic cholangiocarcinoma [20] as in the two cases experienced in this series. The most difficult lesions to assess and make treatment recommendations for are peripheral ductal lesions which do not cause jaundice but are found coincidentally or cause cholestasis. In these patients often the only finding is a short segment of dilated intrahepatic duct. In this series 5/9 of these patients were found to have a cholangiocarcinoma on final histology, and surgery for these lesions is therefore justified, particularly as these lesions can usually be resected safely without the need for resection of the extrahepatic biliary tree.

A particularly difficult group of patients to assess and make treatment recommendations for is the group of predominantly young women with primary liver lesions where the differential diagnosis includes hepatoma, adenoma, and

focal nodular hyperplasia. These lesions are usually single but may be multifocal and often occur on a background of obesity or oral contraceptive use [30]. In this series 6/10 lesions were shown to be neoplastic on final histology (adenoma or hepatoma) and surgery appears justified in this patient group.

Overall 5% of patients underwent surgery for misdiagnosed benign lesions, which is similar to earlier experience [31]. The most common benign lesions were haemangiomas which can be hypo-, iso-, or hyperattenuating on imaging and can sometimes increase in size [25], making distinction from malignant tumours difficult.

In conclusion approximately 10% of patients proceeding to surgery following discussion at the HPB MDT are subsequently shown to have an inaccurate diagnosis and 5% are understaged. Despite an increase in the number of imaging modalities used, there has been no change in this rate over time. These discrepancies must be considered in the context of the risk of overstaging resectable disease or misdiagnosing malignant lesions as benign.

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The pre-operative rate of growth of colorectal metastases in patients selected for liver resection does not influence post-operative disease-free survival

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Abstract

Aims: To assess the potential association between the change in diameter of colorectal liver metastases between pre-operative imaging and liver resection and disease-free survival in patients who do not receive pre-operative liver-directed chemotherapy.

Materials and methods: Analysis of a prospectively maintained database of patients undergoing liver resection for colorectal liver metastases between 2005 and 2012 was undertaken. Change in tumour size was assessed by comparing the maximum tumour diameter at radiological diagnosis determined by imaging and the maximum tumour diameter measured at examination of the resected specimen in 157 patients.

Results: The median interval from first scan to surgery was 99 days and the median increase in tumour diameter in this interval was 38%, equivalent to a tumour doubling time (DT) of 47 days. Tumour DT prior to liver resection was longer in patients with T1 primary tumours (119 days) than T2-4 tumours (44 days) and shorter in patients undergoing repeat surgery for intra-hepatic recurrence (33 days) than before primary resection (49 days). The median disease-free survival of the whole cohort was 1.57 years (0.2–7.3) and multivariate analysis revealed no association between tumour DT prior to surgery and disease-free survival.

Conclusions: The rate of growth of colorectal liver metastases prior to surgery should not be used as a prognostic factor when considering the role of resection.

Keywords: Liver; Metastasis; Colorectal; Resection

Introduction

Although the survival of patients with untreated metastatic colorectal cancer has been described[1] the rate of growth of untreated colorectal liver metastases (CRLM) has not been defined, as patients will either receive active treatment or be treated with palliative intent where assessment of tumour progression is rarely undertaken. CRLM may sustain a period of growth between diagnosis and treatment, and assessment of change in tumour size in this period allows an estimate of growth rate. Liver resection provides a potential cure for patients with CRLM with five-year survival rates ranging from 32 to 65%.[2,3] Factors shown to affect survival include CEA estimation,[4] tumour number,[4–6] tumour size,[4,6,7] resection margin involvement,[4,6,8] the presence of satellite lesions,[9] the ratio of

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neutrophils to lymphocytes in peripheral white blood cells[10] and the response to liver-directed chemotherapy.[11] Little information however is available regarding the influence of the pre-operative rate of growth of CRLM, often expressed as tumour doubling time (DT), on survival following liver resection.

The aim of this study was to assess the DT of CRLM in patients not receiving liver-directed chemotherapy between radiological diagnosis and liver resection and to explore potential associations with tumour recurrence and survival after resection.

Materials and methods

Analysis of data retrieved from a prospectively maintained database of 319 patients undergoing liver resection for CRLM between May 2004 and December 2012 was performed. One hundred and fifty five patients receiving liver-directed chemotherapy were excluded. Imaging was performed with either computerised tomography (CT) or magnetic resonance imaging (MRI) and reviewed at the specialist HPB MDT. The diameter of the largest lesion was measured and recorded in the database for research purposes. Change in tumour size was assessed by comparing the maximum tumour diameter at radiological diagnosis and the maximum tumour diameter measured at examination of the resected specimen. Change in size was expressed as a function of time. Tumour DT was calculated using the equation:

$$DT = Ti \times Log2/(3 \times Log(Dp/Dr)$$

where Ti = time interval between radiological diagnosis and surgery, Dp = diameter at pathology and Dr = diameter at radiological diagnosis.[12]

Data relating to primary and secondary tumour pathology and other routine clinical information were retrieved. Liver resections were defined according to the Brisbane classification[13] and undertaken using standard techniques. Major resections were defined as resections of four or more segments.[14] Synchronous metastases were defined as those diagnosed prior to or within two months of primary surgery. Post-operative follow-up included surveillance CT scans at six-monthly intervals for three years and annually to five years after resection. The timing and site of tumour recurrence were recorded as well as dates of death. Follow-up was completed at March 2014.

Patients were excluded from survival analysis if they died without undergoing surveillance imaging or underwent palliative resections. Patients who developed tumour recurrence at the resection surface following a resection with a positive margin (R1) were excluded as these were deemed to have been due to technical failure rather than tumour recurrence.

Survival curves were constructed by the Kaplan–Meier method and differences in survival were assessed using the log rank method. Comparison between groups was performed using chi-square for categorical variables or Kruskal–Wallis test for continuous variables. Potential associations between pre- and intra-operative factors, as well as histological outcome and tumour recurrence were tested using univariate logistic regression for continuous variables or chi-square for discrete variables test at the level of $P < 0.25$.[15] Significant variables in the univariate analysis were included in the multivariate logistic regression model and were considered to be significant if $P < 0.05$. Univariate and multivariate analyses were carried out using the statistical package R 2.1.14.[16]

Ethical approval for the study was obtained from the South West Health Research Authority. Formal Research Ethics Committee review was not required because patient data were collected in the course of their normal hospital care and were anonymised for research purposes. No patient consent was required for this study.

Results

During the study period 164 liver resections were performed for CRLM in 160 patients who did not receive pre-resection liver-directed chemotherapy. In seven cases no pre-operative imaging was available, leaving 157 resections for analysis, including 79 (50.3%) major and 78 (49.7%) minor resections. Details of patients undergoing surgery are displayed in Table 1. In sixty-six cases (42.0%), patients received adjuvant chemotherapy following primary colorectal surgery, of whom 19 (28.8%) were treated with 5-FU, 18 (27.3%) with capecitabine, 10 (15.2%) with capecitabine and oxaliplatin, two with capecitabine and bevacizumab and one with 5-FU and oxaliplatin. Details of the post-primary surgery adjuvant regime were not available in 16 patients (25%). The median number of cycles of adjuvant chemotherapy was six (1–8). The median interval between primary colorectal resection and the diagnosis of metachronous tumours was 15 months (3 months–7.9 years).

The median interval from diagnosis of CRLM to liver resection was 99 days (20–548 days). CRLM were diagnosed by MRI in one patient and by CT in 156 patients (99%). The median diameter of the largest tumour was 25 mm (5–110) at diagnosis and 35 mm (3–155) in the resection specimen ($P < 0.001$). The median change in diameter during this interval was +38% (−92% to +518%) and the median rate of increase in maximum tumour diameter was 2.92% per week (−7.0% to +37.7%) (Fig. 1). In 27 patients (17.2%) the maximum tumour diameter in the resection specimen was smaller than that determined by pre-operative imaging. The median calculated tumour DT was 47 days (−743 to 1081 days).

Table 1
Characteristics of 157 patients undergoing resection for CRLM showing tumour doubling time in subsets.*Significant at $P < 0.05$.

N = 157		Median (range)	Count (%)	Tumour doubling time (days)	Pearson's correlation coefficient	P-Value
Age		69 (34–90)			−0.041	0.613
Gender	Female		52 (33.1)	45 (−398 to +1081)		0.632
	Male		105 (66.9)	48 (−743 to +803)		
T stage of primary	0		1 (0.6)	231		0.035*
	1		6 (3.8)	119 (69 to 190)		
	2		10 (6.4)	40 (−166 to +278)		
	3		96 (61.1)	47 (−493 to +511)		
	4		38 (24.2)	44 (−743 to +1081)		
	Not available		6 (3.8)			
N stage of primary	0		79 (50.3)	45 (−602 to +511)		0.070
	1		49 (31.2)	58 (−509 to +1081)		
	2		25 (15.9)	35 (−743 to +803)		
	Not available		4 (2.5)			
V stage of primary	0		78 (49.7)	45 (−743 to +803)		0.215
	1		41 (26.1)	49 (−167 to +1081)		
	Not available		38 (24.2)			
Duke's Stage of primary	A		11 (7.0)	73 (−52 to +231)		0.054
	B		65 (41.4)	44 (−603 to 511)		
	C		77 (49.0)	48 (−743 to +1081)		
	Not available		10 (6.4)			
Apical node status of primary	Positive		13 (8.3)	34 (−166 to +803)		0.284
	Negative		121 (77.1)	47 (−743 to +511)		
	Not available		23 (14.6)			
Differentiation of primary	Well/moderate		39 (24.8)	51 (−493 to +803)		0.462
	Moderate		59 (37.6)	46 (−509 to +511)		
	Moderate/poor		4 (2.5)	32 (−743 to +44)		
	Poor		8 (5.1)	34 (−167 to +169)		
	Not available		47 (29.9)			
Site of primary	Colonic		74 (47.1)	47 (−743 to +803)		0.613
	Rectal		83 (52.9)	48 (−493 to +1081)		
Timing of liver metastases	Synchronous		28 (17.8)	38 (−336 to +189)		0.444
	Metachronous		129 (82.2)	48 (−743 to +1081)		
Previous adjuvant chemotherapy	Yes		66 (42.0)	48 (−743 to +803)		0.979
	No		91 (58.0)	44 (−603 to +1081)		
Repeat operation	Yes		23 (14.6)	33 (−743 to +1081)		0.050*
	No		134 (85.4)	49 (−603 to +803)		
Number of liver lesions		1 (1–9)			−0.051	0.529
Diameter of largest metastasis at diagnosis (mm)		25 (5–110)			0.019	0.816
Differentiation of liver metastases	Well		1 (0.6)	69		0.768
	Well/moderate		33 (21.0)	54 (−202 to +278)		
	Moderate		77 (49.0)	43 (−743 to +1081)		
	Moderate/poor		1 (0.6)	60		
	Poor		2 (1.3)	145 (+10 to +280)		
	Not stated		43 (27.4)	48 (−603 to +803)		
Vascular invasion of liver metastases (microscopic)	Yes		28 (17.8)	45 (−603 to +189)		0.715
	No		129 (82.2)	47 (−743 to +1081)		

Assessment of potential associations between tumour DT and other patient factors revealed an association with primary tumour stage ($P = 0.035$). The median tumour DT was longer in patients with T1 tumours (119 days) compared to those with T2 (40 days), T3 (47 days) and T4 (44 days) tumours. Tumour DT was shorter in patients undergoing repeat liver resection (33 vs. 49 days) (Table 1).

Seventeen patients were excluded from survival analysis because they underwent non-curative resection ($n = 7$), developed cut surface recurrence after an R1 resection ($n = 3$) or did not undergo surveillance imaging ($n = 7$), leaving 140 patients for analysis. At closure of the study the median follow-up was 1.2 years (0.2–7.3). Eighty-one patients (57.9%) suffered tumour recurrence within the study period, and there were 48 deaths (34.3%). The median disease-free survival of the group was 1.57 years. Analysis of quartiles determined by tumour DT prior to surgery revealed that DT was not associated with disease-free survival

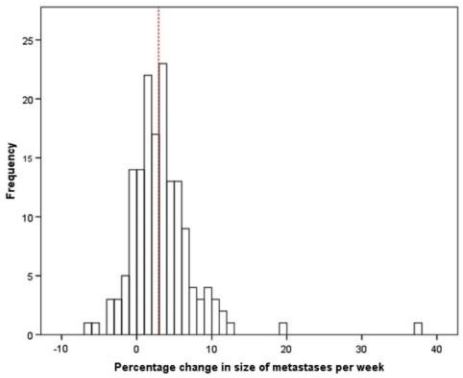


Figure 1. Rate of change in tumour size from diagnosis to resection in 157 patients with colorectal liver metastases. Median change in size = +2.9% per week (−7.0% to +37.7%).

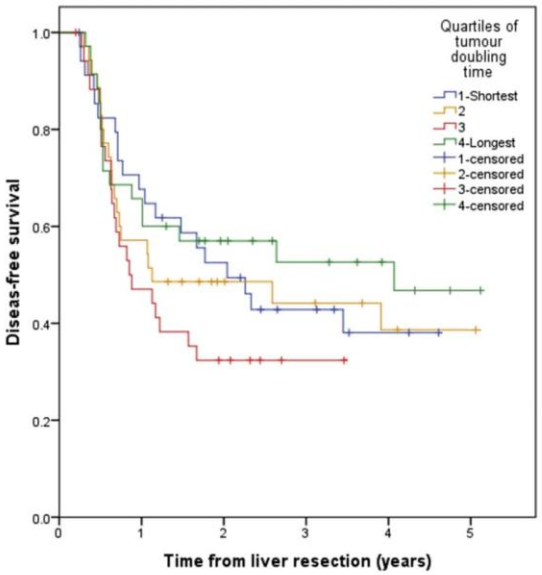
after surgery (P = 0.182) (Fig. 2). Multivariate analysis of pre-operative factors including rate of growth of CRLM revealed that the only significant predictor of tumour recurrence was the number of metastases resected (Table 2). For each extra metastasis the risk of recurrence increased by a factor of 1.3 (P = 0.013). Tumour DT was not found to be an independent predictor of tumour recurrence (P = 0.593).

Discussion

Despite the wealth of information relating to prognostic factors which affect survival after resection of CRLM the lack of data relating to tumour DT is surprising. Tumour DT has been shown to be a significant prognostic factor in the treatment of many solid tumours in including hepatocellular carcinoma,[17] sarcoma,[18] renal cancer,[19] lung cancer[20] and gynaecological cancer.[21] A study estimating the rate of growth of CRLM used early CT scans in patients not undergoing treatment and found a DT of 112 days.[22] More recently DT of CRLM was estimated by serial scans prior to resection in eight patients and a median DT of 63 days was found.[23] Tumour DT was found to be associated with poorer survival after resection. Estimates of DT of CRLM have also been made by assessment of the DT of serum concentration of CEA,[23–25] which have revealed a DT of 10−411 days.[23,25] The tumour DT determined by CEA was found to be the most significant marker of outcome following resection in 144 patients.[24] A correlation of increasing CEA secretion with tumour growth has been demonstrated only in animal studies,[26,27] and many CRLM do not secrete the marker.[23] Estimation of DT in pulmonary CR metastases is commonly performed, as serial imaging is frequently undertaken in this situation. The range of DT has been reported as 29−385 days[28,29] and a tumour DT of less than 100 days has been shown to be associated with increased risk of intrapulmonary recurrence following lung resection.[30] Other studies have shown the difficulty of estimating DT in primary colorectal cancer based on changes in tumour size.[31]

The main finding of clinical significance from this study is that, in contrast to the treatment of many other solid tumours, and colorectal metastases in the lung, the rate of growth of CRLM has no influence on survival after resection. The proportion of patients with CRLM who are offered liver resection is small (10−20%)[32,33] and patients undergo a selection process before being offered liver resection. In the majority of cases this involves exclusion of patients with extra-hepatic disease, rapidly progressive disease and where there is extensive replacement of the liver with tumour. Furthermore this selection process may have involved a 'trial of time' in the early part of this study, which may account for the relatively long interval between diagnosis of liver metastases and liver resection. It is likely that this selection process retains a subset of patients with low-volume, liver-only metastases, whose disease remains temporarily localised to the liver. This finding supports the view that the liver provides a special site of containment of metastatic disease in some patients, in whom surgical resection is likely to be effective.[34] Studies of genetic biomarkers and apoptosis have also revealed that CRLM generally have lower rates of cellular proliferation than primary colorectal cancer.[35,36]

A weakness of the study is the comparison of tumour diameter measured radiologically with pathological findings. This method may be subject to error as the accuracy of CT scan in determining diameter of CRLM has not been demonstrated. Correlation of CT measurement with pathological findings has been performed for hepatoma, and CT scans have been shown to overestimate the size of these lesions.[37] The tumour margin of CRLM may be infiltrative and less clearly defined than that of hepatoma,[38,39] although some lesions have a clearly defined capsular margin.[40] A degree of subjectivity may be necessary in undertaking a comparison of radiological and pathological findings and it is possible that CT scans underestimate the size of CRLM, which may account for some of the difference in size seen between imaging and pathological examination. Measurement of a single tumour diameter is however a valid technique and has been shown to correlate well with tumour volume.[41] The large change in tumour diameter (38%) over a long time period (99 days) and the normal appearance of the frequency distribution of changes in diameter in our study however support the validity of the method. Survival after liver resection may be affected by further chemotherapy, and details of chemotherapy administered to patients between liver resection and death are not available, as this treatment may have been administered in other centres. The rate of growth of



Quartile 1 Shortest						
Number at risk	35	23	17	11	7	
Number of events		11	5	3	1	
Quartile 2						
Number at risk	35	20	12	10	7	6
Number of events		15	3	1	1	0
Quartile 3						
Number at risk	35	16	10	6		
Number of events		18	5	0		
Quartile 4 Longest						
Number at risk	35	23	16	12	9	6
Number of events		12	3	1	0	1

Figure 2. Kaplan–Meier disease-free survival curves according to tumour doubling time quartiles among 140 patients with CRLM not treated with liver-directed chemotherapy (Log rank P = 0.309).

tumours prior to resection is however not measured in this unit and this feature is unlikely to have led to bias by influencing oncologists in the administration of chemotherapy. Adjuvant chemotherapy following liver resection is also unlikely to have been administered to this patient group as it is not included in our local protocol for the treatment of CRLM without a trial of liver-directed neo-adjuvant treatment.

Although resection for CRLM is mainly offered to patients with disease confined to the liver, tumour recurrence occurs in the majority. Attempts to predict outcome based on morphological characteristics of the liver metastases have met with limited success as they rely on these characteristics being a surrogate for biological behaviour and metastatic potential. Few studies have been undertaken to correlate tumour characteristics with biological markers of aggressiveness, although a long tumour DT has been shown to be associated with a favourable host immune response.[23] This study reveals that among selected patients with liver-only disease the rate of tumour growth of CRLM prior to surgery does not influence post-operative survival, and should not be regarded as an adverse factor when considering the role of liver resection in this patient group.

Table 2
Univariate and multivariate analysis of factors associated with tumour recurrence following liver resection for CRLM in 140 patients not treated with liver-directed chemotherapy.

N = 140		Not recurred (n = 59)		Recurred (n = 81)		Univariate analysis		Multivariate analysis	
		Median (range)	Count (%)	Median (range)	Count (%)	P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)
Age		69 (51–84)		68 (34–87)		0.786			
Gender	Male		43 (72.9)		53 (65.4)	0.349			
	Female		16 (27.1)		28 (34.6)				
T stage of primary	0		1 (1.7)		0	0.560			
	1		0		5 (6.2)				
	2		4 (6.8)		6 (7.4)				
	3		35 (59.3)		48 (59.3)				
	4		17 (28.8)		19 (23.5)				
	NA		2 (3.4)		3 (3.7)				
N stage of primary	0		29 (49.2)		42 (51.9)	0.635			
	1		21 (35.6)		23 (28.4)				
	2		8 (13.6)		14 (17.3)				
	NA		1 (1.7)		2 (2.5)				
V stage of primary	0		26 (44.1)		46 (56.8)	0.133[a]		0.203	0.52 (0.19–1.42)
	1		18 (30.5)		17 (21.0)				
	NA		15 (25.4)		18 (22.2)				
Duke's Stage of primary	A		4 (6.8)		6 (7.4)	1.000			
	B		24 (40.7)		34 (42.0)				
	C		29 (49.2)		39 (48.1)				
	NA		2 (3.4)		2 (2.5)				
Apical node of primary	Positive		3 (5.1)		9 (15.3)	0.313			
	Negative		43 (72.9)		64 (79.0)				
	NA		13 (22.0)		8 (9.9)				
Site of primary	Colon		29 (49.2)		36 (44.4)	0.704			
	Rectum		30 (50.8)		45 (55.6)				
Timing of metastases	Syn		8 (13.6)		16 (19.8)	0.339			
	Met		51 (86.4)		65 (80.2)				
Previous adjuvant chemotherapy			25 (42.4)		34 (42.0)	0.962			
Repeat operation			9 (15.3)		11 (13.6)	0.780			
Wedge resection included			22 (37.3)		33 (40.7)	0.812			
Radiofrequency ablation included			1 (1.7)		1 (1.2)	0.821			
Tumour doubling time (DT)		47.4 (−743 to +1081)		47.6 (−602 to +803)		0.957	0.98 (0.50–1.94)		
Number of liver lesions		1 (1–3)		1 (1–9)		0.073[a]	1.54 (0.96–2.46)	0.013[b]	1.30 (1.06–1.59)
Diameter of largest metastasis at diagnosis (mm)		35 (8–155)		40 (3–120)		0.202[a]	1.01 (1.00–1.02)	0.854	1.00 (0.98–1.02)
Positive resection margin (R1)			10 (16.9)		12 (14.8)	0.699			
Differentiation of liver metastases	Well/mod		10 (16.9)		15 (19.8)	0.801			
	Mod		33 (55.9)		38 (46.9)				
	Mod/poor		0		1 (1.2)				
	Poor		0		2 (2.5)				
	Not stated		16 (27.1)		24 (29.6)				
Vascular invasion of liver metastases (microscopic)	Yes		8 (13.6)		15 (18.5)	0.495			
	No		51 (86.4)		66 (81.5)				

NA = no data available.
[a] Significant at the level of 0.25 for univariate analysis and included in multivariate analysis.
[b] Significant at the level of 0.05 for multivariate analysis.

Conflict of interest

The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Rebound growth of hepatic colorectal metastases after neo-adjuvant chemotherapy: effect on survival after resection

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Abstract

Background: A period of recovery is commonly allowed between completion of chemotherapy for colorectal liver metastases (CRLM) and resection, during which tumour progression may occur. The study-aim is to assess the growth of CRLM in this interval and association with outcome.

Method: Data on 146 patients were analysed. Change in tumour size was assessed by comparing size determined by imaging performed on completion of chemotherapy with that determined by examination of the resected specimen, categorised by RECIST criteria.

Results: In the interval before surgery sixteen patients (11%) fulfilled criteria for partial response (PR), 48 (33%) had stable disease (SD) and 82 (56%) had progressive disease (PD). Among patients with PD following chemotherapy the median disease-free survival of patients who initially responded (26 months) was longer than in those who initially had stable disease (7 months) (P = 0.002). No association was noted between rate of tumour growth after completion of chemotherapy and disease-free survival.

Conclusion: Change in tumour size after completion of chemotherapy is variable and can be rapid, especially in patients who initially respond to treatment. However, disease-free survival is determined by tumour behaviour during treatment and not by change in size after completion of chemotherapy.

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Introduction

Liver resection provides a potential cure for patients with colorectal liver metastases (CRLM), with five-year survival rates ranging from 32 to 65%.[1] Neo-adjuvant systemic chemotherapy has been advocated in patients with initially resectable[2,3] and unresectable[4–6] CRLM. Tumour response to chemotherapy is usually assessed by CT scans undertaken after treatment and some studies have suggested that surgery should not be performed when progression on chemotherapy occurs, as the outcome is poor.[7,8] Although the proportion of patients with CRLM who respond to chemotherapy has been defined in many studies[3,9] the duration over which the changes are sustained following completion of treatment has not been described, and the consequences of tumour progression in the interval between completion of chemotherapy and surgery are unknown. As chemotherapy can cause significant hepatotoxicity[10,11] it is common practice to allow a chemotherapy-free interval for these changes to reverse before undertaking liver resection,[12] potentially allowing uninhibited tumour progression. The aim of this

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study was to assess the change in size of CRLM between post-chemotherapy imaging and liver resection and to measure potential associations with tumour recurrence and survival.

Methods

Analysis of data retrieved from a database of all patients undergoing liver resection for CRLM between May 2004 and December 2012 was performed. Systemic chemotherapy was administered to patients with radiological evidence of CRLM, where liver resection was planned, according to local protocols. The diameter of the largest metastasis was measured by CT scan and response to chemotherapy graded by RECIST criteria.[13] Any further change in tumour size between completion of chemotherapy and liver resection was measured by comparing the maximum tumour diameter determined by post-chemotherapy imaging and the maximum diameter determined by examination of the resected specimen, expressed as a function of time. Time intervals are expressed in weeks with inter-quartile range (IQR). For purposes of comparison changes in size during this interval were also graded by RECIST criteria. Tumour doubling-time (DT) was calculated using the equation:

$$DT = Ti \times \mathrm{Log}\, 2 / (3 \times \mathrm{Log}(Dp/Dr))$$

where Ti = time interval between post-chemotherapy imaging and surgery, Dp = diameter at pathology and Dr = diameter measured by imaging.[14]

Data relating to primary tumour pathology, the use of adjuvant chemotherapy for primary colorectal cancer, systemic chemotherapy administered for CRLM and other clinical information were retrieved. Synchronous metastases were defined as those diagnosed prior to, or within two months of primary surgery. Liver resections were performed according to the Brisbane classification[15] and undertaken using standard techniques. Post-operative follow-up included surveillance CT scans performed at six-monthly intervals for three years and annually to five years after resection. The timing and site of tumour recurrence were recorded as well as dates of death. Follow-up was completed in March 2014.

Patients were excluded from disease-free survival analysis if they died without undergoing surveillance imaging, or underwent planned non-curative resections. Patients who developed resection-margin recurrence following resection with margin-involvement (R1) were also excluded as these were deemed to have been due to technical failure rather than tumour recurrence.

Survival curves were constructed by the Kaplan–Meier method and differences in survival assessed using the log rank method. Comparison between groups was performed using chi square for discrete variables and Mann Whitney U test for continuous variables. In survival analyses patients who suffered PD after completion of chemotherapy were split into quartiles according to the rate of increase in size of the largest tumour.

Ethical approval for the study was obtained from the South West Health Research Authority. Formal Research Ethics Committee review was not required because patient data were collected in the course of normal hospital care and were anonymised for research purposes.

Results

During the study period 155 patients were treated with neo-adjuvant chemotherapy prior to liver resection. Details of patients undergoing surgery are shown in Table 1 and details of chemotherapy regimes in Table 2. The median number of cycles of chemotherapy administered was 4 (interquartile range 4–6). Three patients received second-line chemotherapy. Nine patients were excluded from response analysis because imaging was not available, leaving 146 patients. The median interval between pre- and post-chemotherapy scans was 15.3 weeks (12.0–20.4) and the median change in diameter of the largest liver metastases during this period was a reduction of 24% (−100% to +342%), or −1.3% (−9.6% to +12.6%) per week. Sixty-four patients (43.8%) fulfilled the RECIST criteria for partial response (PR) and eight patients (5.4%) had a complete response to treatment. Forty-eight patients (32.8%) had stable disease (SD) and twenty-six patients (17.8%) suffered progressive disease (PD). The median reduction in tumour size in patients who responded to treatment was −3.2% (−9.6% to −0.9%) per week.

The median interval between post-chemotherapy imaging and liver resection was 10.4 weeks (7.1–17.6 weeks), and was similar across patient groups regardless of response to chemotherapy (Table 3). During this period the largest tumour diameter

Table 1 Characteristics of 155 consecutive patients undergoing resection for colorectal liver metastases after receiving systemic chemotherapy

N = 155		Median (range)	Count (%)
Age		65 (33–83)	
Gender	Female		67 (43.2)
	Male		88 (56.8)
Timing of liver metastases	Synchronous		120 (77.4)
	Metachronous		35 (22.6)
Previous adjuvant chemotherapy	Yes		23 (14.8)
	No		132 (85.2)
Repeat operation	Yes		5 (3.2)
	No		150 (96.8)
Number of liver lesions		2 (0–10)	
Diameter of largest metastasis at diagnosis (mm)		25 (6–130)	

Table 2 Systemic chemotherapy regimens and response to treatment for 155 patients undergoing liver resection for colorectal liver metastases

N = 155			Count (%)
Chemotherapy regime	Oxaliplatin and capecitabine		118 (76.1)
	5-FU alone		1 (0.6)
	Oxaliplatin and 5-FU		15 (9.7)
	Irinotecan		6 (3.9)
	Capecitabine alone		11 (7.1)
	Notes unavailable		4 (2.6)
	Number of cycles		4 (1–18)
Biological agent	Yes	Cetuximab	7 (4.5)
		Bevacizumab	2 (1.3)
	No		142 (91.6)
	Unknown		4 (2.6)
Dose reduction	Yes		21 (13.5)
	No		134 (86.5)
Change in size of largest tumour on imaging according to RECIST	Complete or partial response		72 (46.5)
	Stable disease		48 (31.0)
	Progressive disease		26 (16.8)
	No imaging available		9 (5.8)

increased in 102 patients (69.9%) and decreased in 37 (25.3%) with a median change of +2.3% per week (−11.1 to +28.0%). By RECIST criteria sixteen patients (10.9%) had PR, 48 patients (32.9%) had SD and 82 patients (56.2%) had PD in the interval before surgery. The increase in tumour diameter was greatest in patients who had a partial or complete response while receiving chemotherapy (Table 3). Of the 120 patients who had either PR or SD whilst receiving chemotherapy only 51 (42.5%) remained in either of these two categories whilst awaiting surgery. Thirteen of 26 patients (50%) who had PD while receiving chemotherapy suffered continued disease progression in the interval to surgery, and only one patient had a late response. The rate of change in size of largest tumour during this interval was 2.3% per week, (−11.1 to +28.0%) which was significantly greater than during the treatment interval (−1.3%, −9.6% to +12.6%) (P = 0.007). The median doubling time of tumours which increased in size during this period was 45.5 days (0.7–1869).

In survival analysis 11 patients were excluded because surgery was deemed non-curative or a staged resection was not completed, and three patients were excluded because they died without undergoing surveillance imaging. Seven patients were excluded because they developed cut-surface recurrence after R1 resection leaving 125 patients for analysis, of whom 104 patients initially had PR or SD. At closure of the study the median follow-up was 36 months (1–97 months). Seventy-nine patients (63.2%) suffered tumour recurrence and there were 45 deaths (36%). Tumour response whilst receiving chemotherapy was associated with significantly longer disease-free survival than PD or SD (Fig. 1a).

Among the 60 patients who initially responded and 44 patients who had stable disease whilst receiving chemotherapy disease-free survival was similar regardless of tumour behaviour after completion of treatment (Fig. 1b and c, respectively). Among the patients who suffered PD in the interval after completing chemotherapy survival was determined by initial response to treatment. In 35 patients who initially responded the median disease-free survival was 26 months (range 2–84), compared to 7 months (range 1–54) in 22 patients who initially had stable disease (P = 0.002). Among the total group of 66 patients who suffered PD after completion of chemotherapy in whom survival analysis was undertaken the rate of increase in size of the largest tumour was not associated with disease-free survival (Fig. 1d).

Discussion

The principle findings of this study are that:

1 tumour response to chemotherapy is associated with improved disease-free survival after resection of CRLM
2 in a large proportion of these patients the treatment effect is transient and disease progression occurs rapidly after stopping therapy
3 the change in tumour size is more rapid after completion of chemotherapy than during treatment

Table 3 Change in maximum diameter of liver metastases among 146 patients during interval between post-chemotherapy imaging and liver resection, categorised according to initial response

Initial response (n = 146)		Complete or partial response (>30%) (n = 72)	Stable disease (n = 48)	Progressive disease (>20%) (n = 26)	P-value CR and PR vs PD
Median interval in weeks from post chemotherapy imaging to liver resection (range)		10 (1–98)	10 (1–54)	10 (1–54)	0.570
Median % change in diameter (range)		+42 (–100 to +838)	+22 (–100 to +157)	+22 (–38 to +156)	<0.001
Change in diameter after completion of chemotherapy (%)	Further response	7 (9.7)	8 (16.6)	1 (3.8)	0.258
	Stable disease	20 (27.8)	16 (33.3)	12 (46)	
	Progressive disease	45 (62.5)	24 (50)	13 (50)	

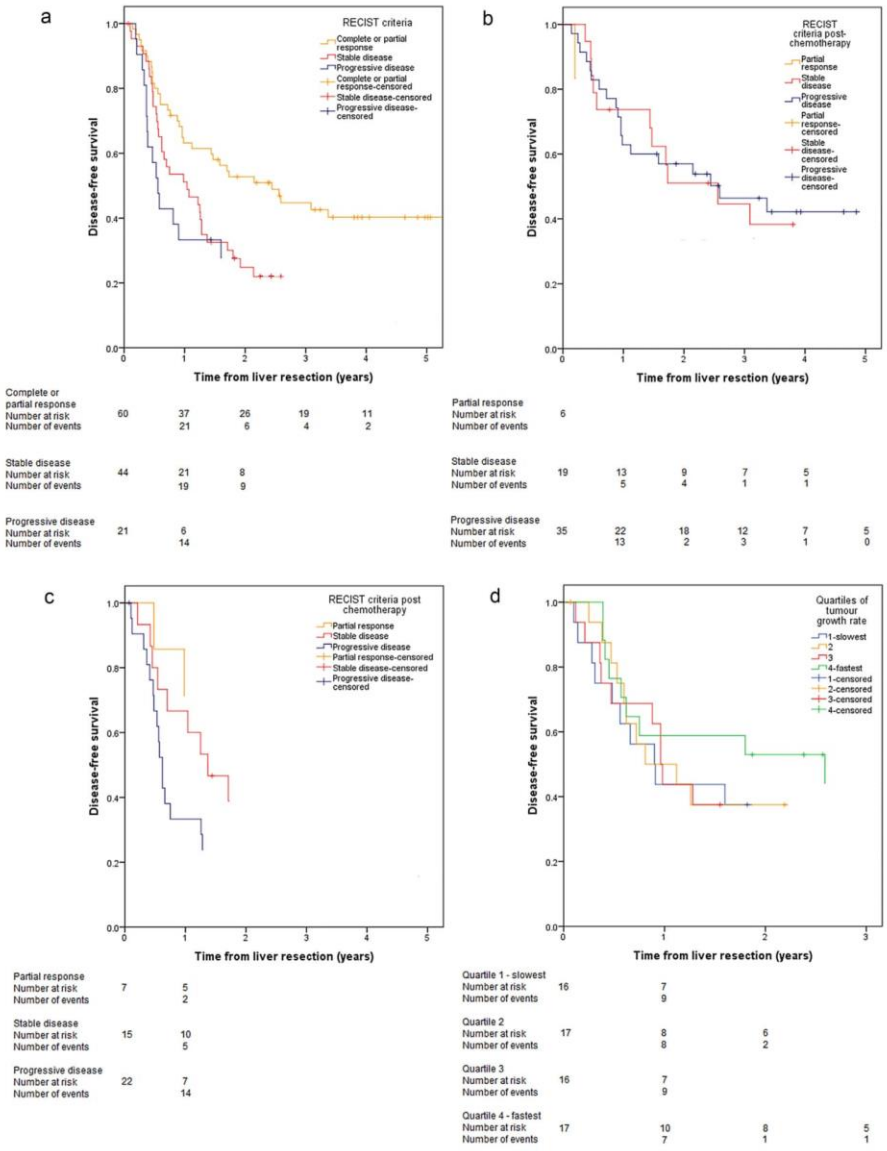

Figure 1 Kaplan–Meier disease-free survival curves following liver resection for colorectal liver metastases for: a) 125 patients treated with pre-operative systemic chemotherapy, determined by response to treatment (log rank P = 0.003), b) 60 patients who initially had partial or complete

4 relative change in tumour size after completion of chemotherapy is not associated with disease-free survival

Although a regime of six cycles of oxaliplatin and capecitabine has been recommended as neo-adjuvant treatment prior to liver resection,[3] the most common regime adopted in this series was four cycles. This regime has been used to minimise complications due to hepatotoxicity which can occur following use of these agents.[11] The association of response to neo-adjuvant chemotherapy estimated by RECIST criteria with improved disease–disease free survival compared to progressive disease has been shown previously,[7,8,16] though others have shown no association.[9]

In keeping with other units a period of recovery is allowed after completion of chemotherapy to minimise the risks of hepatotoxicity. The optimum period of recovery has not been defined but four weeks has been recommended based on studies of the recovery of hepatic clearance of indocyanine green.[17] In the present study the median interval between completion of chemotherapy and surgery was 10 weeks. This period includes the time needed for notification of completion of chemotherapy, MDT discussion, clinic appointments and preparation for surgery. No previous study has addressed the change in tumour size during this period and potential associations with outcomes for patients after surgery. The majority of patients who initially responded to chemotherapy or had stable disease will suffer disease progression after completion of chemotherapy. For tumours which increase in size in this interval the rate of growth is very rapid (2.3% per week), with a calculated tumour DT of 46 days. The DT of untreated CRLM has been reported previously as between 63 and 112 days.[18,19] This rapid tumour growth does not however appear to influence disease-free survival after resection, which is determined by the initial response to chemotherapy. Among the group of patients who suffer disease progression in the interval to surgery the median disease-free survival of patients who initially responded (26 months), is greater than that of patients who initially had stable disease (7 months) ($P = 0.002$).

The lack of survival effect of rebound growth in tumour size after completion of chemotherapy is unusual in the context of the expected behaviour of solid tumours. There is evidence that rapid tumour proliferation is associated with poor outcome in colorectal cancer, although these studies have usually employed molecular kinetic markers.[20–22] Despite these findings there is little evidence that in vitro markers of tumour proliferation correlate with macroscopic tumour growth or that the growth rate of CRLM correlates with poor outcome after resection. It is possible that the increase in tumour size noted after cessation of chemotherapy represents tumour swelling, rather than growth of viable tumour cells, and tumour expansion may be associated with cell death.[23] The change in size of CRLM may also not be representative of extra-hepatic effects. Tumour recurrence after resection of CRLM is caused by micro-metastases not detected at the time of initial treatment[24,25] and response to treatment of these malignant cells may be more sustained than that by large liver metastases. In this context change in size of CRLM can be seen as a surrogate marker for the effects of chemotherapy on peripheral micrometastases only during treatment. Decrease in size of these lesions may indicate a beneficial effect in terms of micrometastatic disease, whereas rebound growth of hepatic lesions after cessation of treatment may not indicate recovery of peripheral micrometastases.

An important question raised by these findings relates to the duration allowed between completion of chemotherapy and liver resection. No trial has been undertaken to address this issue and the risks are not uniform between patients, being affected by the extent of the planned resection and the size of the future liver remnant. Our findings suggest that when chemotherapy is administered to patients with resectable tumours, disease progression after cessation of treatment has no adverse effect on outcome and should not influence the timing of surgery. When chemotherapy is used specifically to down-size CRLM of borderline resectability however rapid tumour progression after cessation of treatment may render the lesions unresectable, and earlier liver resection may be desirable in this group.

The potential weakness of this study relates to the measurement of tumour size. We have compared the maximum tumour diameter measured by imaging with that noted on macroscopic measurement of the resection specimen using a unidimensional measurement, as this has been shown to be representative of tumour volume.[26] This method has not however been previously validated by a direct comparison of tumour size determined by imaging and pathology, and no data are available regarding the accuracy of CT scans in determining the size of CRLM. CT scan measurements however have been shown to be accurate in the measurement of hepatoma.[27] Also the time point at which post-chemotherapy imaging was undertaken was variable, and some change in size may have occurred in the interval between completion of chemotherapy and final imaging. Another potential source of inaccuracy is that we have not included data relating to the use of chemotherapy after surgery in survival analyses. Uptake of adjuvant chemotherapy after liver resection is generally poor, though many patients will have received palliative treatment. Measurement of tumour growth after completion of chemotherapy is not undertaken in clinical practice and this factor is unlikely to have led to bias in the administration of

response to chemotherapy categorised according to tumour behaviour after completion of chemotherapy (PR/SD/PD) ($P = 0.591$), c) 44 patients who initially had stable disease categorised according to tumour behaviour after completion of chemotherapy (PR/SD/PD) ($P = 0.436$), d) 66 patients who suffered tumour progression (PD) after completion of chemotherapy, divided into quartiles according to rate of tumour growth ($P = 0.556$)

chemotherapy to individual patients. The sample size used in this study is also not large, and a study with greater power may reveal differences in survival between groups not apparent in this analysis.

Conclusion

Change in tumour size after completion of chemotherapy is variable and can be rapid, especially in patients who initially responded to treatment. It does not however appear to affect outcome and should not be considered an adverse factor when counselling patients or determining treatment options.

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Conflicts of interest

None declared.

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Research Article

The Interaction between Diabetes, Body Mass Index, Hepatic Steatosis, and Risk of Liver Resection: Insulin Dependent Diabetes Is the Greatest Risk for Major Complications

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Background. This study aimed to assess the relationship between diabetes, obesity, and hepatic steatosis in patients undergoing liver resection and to determine if these factors are independent predictors of major complications. *Materials and Methods*. Analysis of a prospectively maintained database of patients undergoing liver resection between 2005 and 2012 was undertaken. Background liver was assessed for steatosis and classified as <33% and ≥33%. Major complications were defined as Grade III–V complications using the Dindo-Clavien classification. *Results*. 504 patients underwent liver resection, of whom 56 had diabetes and 61 had steatosis ≥33%. Median BMI was 26 kg/m^2 (16–54 kg/m^2). 94 patients developed a major complication (18.7%). BMI ≥ 25 kg/m^2 ($P = 0.001$) and diabetes ($P = 0.018$) were associated with steatosis ≥33%. Only insulin dependent diabetes was a risk factor for major complications ($P = 0.028$). Age, male gender, hypoalbuminaemia, synchronous bowel procedures, extent of resection, and blood transfusion were also independent risk factors. *Conclusions*. Liver surgery in the presence of steatosis, elevated BMI, and non-insulin dependent diabetes is not associated with major complications. Although diabetes requiring insulin therapy was a significant risk factor, the major risk factors relate to technical aspects of surgery, particularly synchronous bowel procedures.

1. Introduction

Liver failure occurs in up to 32% of patients following liver resection [1–5] and is a major contributor to both morbidity [6] and mortality [7]. Liver resection is technically more difficult in patients with parenchymal liver disease [8] and the risks of liver resection are increased due to impaired hepatic regeneration [9].

Nonalcoholic fatty liver disease (NAFLD) is the commonest cause of liver disease in the West [10] and is also the commonest cause of a sustained rise in serum transaminases in patients with no history of chronic liver disease [11]. NAFLD encompasses steatosis (excess accumulation of triglycerides), steatohepatitis (hepatocyte damage, inflammatory infiltrate, and fibrosis), and cirrhosis [12] and can be demonstrated with routine histological staining. NAFLD is associated with diabetes mellitus and obesity [13, 14] which are also undergoing a global epidemic [15, 16]. However, not all patients with obesity and diabetes develop NAFLD and similarly not all patients with NAFLD suffer either diabetes or obesity [17].

Liver-directed chemotherapy is also associated with hepatotoxicity. Steatohepatitis has been shown to occur in 20% of patients who receive irinotecan and 5% of those who receive fluorouracil (5FU) [18], with a resulting increase in

complications after surgery. Oxaliplatin is associated with sinusoidal obstruction syndrome [18, 19]. Recreational alcohol use is also a major cause of hepatic steatosis [20].

A meta-analysis has shown that hepatic steatosis is associated with increased risk of postoperative complications and that moderate and severe steatosis are associated with increased mortality compared to patients with normal liver parenchyma or mild steatosis [21]. However, this analysis is based on four studies, only two of which included both BMI and diabetes in multivariate analyses [8, 22–24]. Obesity, diabetes, and hepatic steatosis often coexist in the metabolic syndrome [25], and the increased risk of operating in the presence of steatosis may be due to associated comorbidity. Diabetes mellitus and obesity are independent risk factors for postoperative complications following other types of major surgery, including infectious [26–28], cardiovascular [28, 29], and renal complications [26, 28, 29]. Furthermore in the four studies included in the meta-analysis heterogeneous definitions of postoperative complications were used, and often relatively minor complications were included. Recently complications after liver surgery have been classified by the Dindo-Clavien system [30], which stratifies severity of complications and allows comparison of outcomes between centres.

The aim of this study was to assess the relationship between the incidence of diabetes, obesity, and hepatic steatosis in patients undergoing liver resection after a period of abstention from alcohol consumption and to determine if these factors are independent predictors of major complications following liver resection, using the Dindo-Clavien system.

2. Materials and Methods

A retrospective analysis of a prospectively maintained database of all patients undergoing liver resection between July 2005 and September 2012 was undertaken. Patient characteristics, laboratory data, and intraoperative details were retrieved. BMI was recorded preoperatively and the cohort was divided into three categories: 18.5–24.99 kg/m^2 (normal), 25–29.99 kg/m^2 (overweight), and ≥30 kg/m^2 (obese). Diabetes was categorised according to the requirement for insulin. The presence of preexisting chronic liver disease was confirmed by histology. American Association of Anesthesiologists (ASA) grade was determined by the responsible anaesthetist and the physiologic score calculated according to the POSSUM system [31]. Selected patients were treated with neoadjuvant chemotherapy. All patients underwent preoperative counselling by a nurse specialist where abstention from alcohol was mandated. This instruction was also contained in a patient information sheet. The normal interval from preoperative counselling to surgery in this series is approximately 30 days.

Liver resections were defined according to the Brisbane classification [32] and undertaken using standard techniques, using hepatic inflow occlusion selectively. Major resections were defined as resections of three or more segments. Synchronous liver and bile-duct resections were performed in the presence of hilar cholangiocarcinoma. Radiofrequency ablation was used where small lesions were not accessible for surgical resection.

Major complications were defined as Grade III–V complications using the Dindo-Clavien classification where Grade III complications are those requiring surgical, endoscopic, or radiological intervention, Grade IV includes life threatening complications including organ failure, and Grade V is death [30]. Posthepatectomy liver failure (PHLF) was defined in accordance with the International Study Group of Liver Surgery (ISGLS) [33] as an increased prothrombin time (PT) and serum bilirubin concentration on or after postoperative day five. In patients with preoperatively increased PT or serum bilirubin concentration PHLF was defined as an increasing serum bilirubin concentration and PT on or after postoperative day 5, compared with the values of the previous day. Renal dysfunction was defined as an increase in serum creatinine of ≥1.5-fold from the preoperative baseline, according to RIFLE criteria [34].

Serum biochemistry tests and coagulation assays were performed preoperatively, in the first 24 postoperative hours, and then repeated according to clinical course. The peak measurement of bilirubin, prothrombin time (PT), and creatinine was recorded. Clotting factors were not administered between postoperative days (POD) 1–5. At histological examination the background liver parenchyma at least 1 cm from the tumour edge was assessed for degree of steatosis using the Brunt classification (the proportion of hepatocytes containing fat droplets; 1: <33%, 2: 33–66%, and 3: >66%) [35]. For analysis the data was divided into <33% (mild or none) and ≥33% (moderate or severe).

The minimum postoperative followup was 90 days and mortality was recorded along with details of postoperative intervention and complications.

To determine potential associations between patient characteristics and steatosis and between patient, operative, and histological characteristics and major complications univariate logistic regression or chi-square test at the level of $P < 0.25$ [36] was performed, as appropriate. Significant variables in the univariate analysis were included in the multivariate logistic regression model and were considered to be significant if $P < 0.05$. All analyses were carried out using the statistical package R 2.1.14 [37].

3. Results

Of 504 patients treated in the study period, surgery was undertaken for metastatic disease in 358 (71.0%), of whom 308 (61.1%) had colorectal liver metastases. Resections were performed for primary hepatic malignancy in 106 patients (21.0%) including hepatocellular carcinoma in 39 (7.7%) and cholangiocarcinoma in 31 (6.2%) patients. In 40 patients (7.9%) resection was performed for benign tumours. Major resection was undertaken in 299 patients (59.3%). In twenty-three patients a synchronous bowel procedure was performed including 10 colonic resections, 11 small bowel procedures, one gastric resection, and one Whipple's procedure. Fifty-six patients were diabetic (11.1%), of whom 15 were insulin dependent (26.8%). The median BMI of patients undergoing resection was 26 kg/m^2 (range 16–54 kg/m^2). Elevated BMI

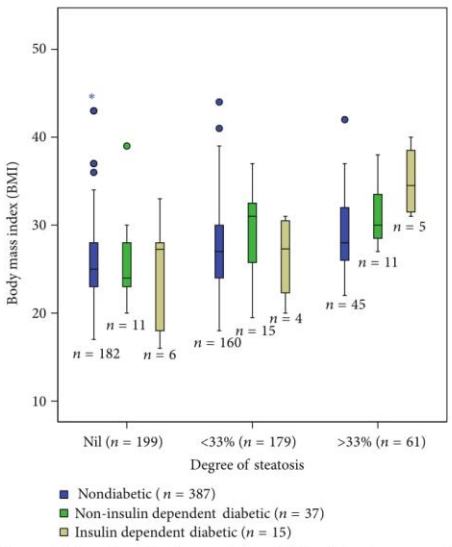

FIGURE 1: Box plot of body mass index (BMI), diabetic status, and degree of hepatic steatosis in 439 patients undergoing liver resection. Nil versus <33% ($P < 0.001$), <33 versus ≥33% ($P = 0.001$).

(≥25 kg/m^2) was noted in 332 patients (65.9%) and 123 patients (24.4%) were obese (≥30 kg/m^2). Five patients had no BMI recorded and were excluded from analysis. Preoperative liver-directed chemotherapy was used in 168 patients (33.3%). The most commonly used regime was oxaliplatin and capecitabine which was used in 118 patients (70.2%). Irinotecan was used in six patients (3.6%).

Histopathological examination revealed zero, mild, moderate, and severe steatosis in 199 (39.5%), 179 (35.5%), 54 (10.7%), and seven (1.4%) patients, respectively. Degree of steatosis was not recorded in 65 patients (12.9%). The distribution of BMI, diabetes, and steatosis is shown in Figure 1. The median BMI of patients with no steatosis (25 kg/m^2, range 16–45) was lower than those with mild steatosis (27 kg/m^2, range 18–44) ($P < 0.001$), which was lower than patients with moderate/severe steatosis (29 kg/m^2, range 22–42) ($P = 0.001$). The median BMI of diabetic patients was 29 kg/m^2 (16–40) compared to 26 kg/m^2 (17–54) in nondiabetic patients ($P = 0.002$). There was no difference in the median BMI of patients with insulin dependent diabetes (IDDM) (29 kg/m^2, range 16–40) and those with non-insulin dependent diabetes (NIDDM) (29 kg/m^2, range 20–39) ($P = 0.816$). The rate of mild steatosis among diabetics was 16/52 (30.8%) compared to 45/387 (11.6%) in nondiabetics ($P = 0.001$), but there was no significant difference in the rates of mild steatosis in patients with NIDDM (11/37) and those with IDDM (5/15). The rate of moderate/severe steatosis was 6/135 (4.4%) in normal weight, nondiabetic patients, 39/249 (15.6%) in overweight nondiabetics ($P = 0.001$), 0/12 in normal weight diabetics, and 15/39 (38.5%) in overweight diabetics ($P < 0.001$).

Elevated preoperative transaminase levels were noted in 18 of 60 patients (30%) with moderate/severe steatosis and 61 of 369 patients (16.5%) with steatosis <33% ($P = 0.019$). The sensitivity and specificity of elevated transaminases for predicting the presence of moderate or severe steatosis were 30% and 83%, respectively.

Multivariate analysis revealed that elevated BMI ≥ 25 kg/m^2 ($P = 0.001$) and the presence of diabetes ($P = 0.018$) were significantly associated with moderate/severe hepatic steatosis (Table 1). BMI ≥ 25 kg/m^2 increased the risk by a factor of 2.97 and diabetes increased the risk by a factor of 2.69. Among diabetic patients insulin dependence increased the risk of moderate/severe steatosis by a factor of 4.31 ($P = 0.037$). However, BMI ≥ 30 kg/m did not increase the risk of moderate/severe steatosis compared to BMI of 25–29.9 ($P = 0.144$). Raised preoperative transaminase levels also increased the risk of moderate/severe steatosis by a factor of 3.82 ($P < 0.001$), and raised preoperative alkaline phosphatase concentrations decreased the risk by a factor of 0.15 ($P = 0.001$). Hepatic steatosis was not associated with liver-directed chemotherapy or other biochemical markers of liver dysfunction (preoperative hypoalbuminemia and hyperbilirubinemia).

During the study period 94 patients developed a major postoperative complication. Twenty-three patients died within 90 days of surgery (4.6%) and 71 patients who survived beyond 90 days suffered a major complication (14.1%). The most common cause of mortality was liver failure (nine patients).

Of patients who developed Grade IV complications 34/64 (53.1%) developed PHLF and 31/64 developed renal failure (48.4%). Of the 34 patients who developed PHLF 29 had undergone major liver resection. Twenty-three patients developed bile leaks, and seven required relaparotomy/relaparoscopy. Multivariate analysis revealed that older age, male gender, hypoalbuminaemia, synchronous bowel procedures, number of segments resected, and blood transfusion were independent risk factors for major postoperative complications (Table 2). There was no association between NIDDM, BMI, or degree of hepatic steatosis and major postoperative complications. IDDM more than trebled the risk of major complication compared to nondiabetics and those with NIDDM. The complications in these groups are shown in Table 3. The greatest risk however occurred when liver resection was undertaken in conjunction with a synchronous bowel procedure, which increased the risk of major complication almost six times that of a liver-only resection. Ten of 23 patients developed major postoperative complications, six of whom had colonic resections (three right sided and three left sided), three had small bowel procedures, and one had a gastric resection.

In the 299 patients who underwent major resection, there was no significant difference in the proportion of patients with steatosis ≥33% between patients who did (10/64, 15.6%) or did not (23/201, 11.4%) develop major complications

Table 1: Analysis of factors associated with hepatic steatosis (≥33%) in 439 patients undergoing liver resection.

$N = 439$	Steatosis < 33% ($n = 378$)		Steatosis ≥ 33% ($n = 61$)		Univariate		Multivariate	
	Median (range)	Count (%)	Median (range)	Count (%)	P value	Comparison	Odds ratio (95% CI)	P value
Age	65 (21–90)		65 (41–87)		0.622			
Gender								
Female		168 (44.4)		24 (39.3)	0.544			
Male		210 (55.6)		37 (60.7)				
Liver-directed chemotherapy								
Yes		132 (34.9)		20 (32.8)	1.000			
No		246 (65.1)		41 (67.2)				
Preexisting chronic liver disease								
Yes		6 (1.6)		3 (4.9)	0.228*			0.869
No		372 (98.4)		58 (95.1)				
Preoperative jaundice (≥50 micromoles/L)								
Yes		5 (1.3)		0	0.800			
No		373 (98.7)		61 (100)				
Hypoalbuminaemia (<35 g/L)								
Yes		15 (4.0)		1 (1.6)				
No		360 (95.2)		59 (96.7)	0.602			
Not recorded		3 (0.8)		1 (1.6)				
Raised preoperative alkaline phosphatase								
Yes		92 (24.3)		5 (8.2)			0.15	
No		283 (74.9)		55 (90.2)	0.008*		(0.05–0.46)	0.001**
Not recorded		3 (0.8)		1 (1.6)				
Raised preoperative transaminase								
Yes		61 (16.1)		18 (29.5)			3.82	
No		308 (81.5)		42 (68.9)	0.021*		(1.85–7.89)	<0.001**
Not recorded		9 (2.4)		1 (1.6)				
Diabetic status								
Nondiabetic		342 (90.5)		45 (73.8)		Diabetic versus nondiabetic	2.69	
Non-insulin dependent		26 (6.9)		11 (18.0)	0.001*		(1.18–6.13)	0.018**
Insulin dependent		10 (2.6)		5 (8.2)		Insulin dependent versus non-insulin dependent	4.31	
							(1.09–16.98)	0.037**
Body mass index (kg/m^2)								
<25		141 (37.3)		6 (10)			2.97	
25–29.9		153 (40.5)		27 (45.0)		<25 versus ≥25	(1.59–5.57)	0.001**
≥30		81 (21.4)		27 (45.0)	<0.001*			
Not recorded		3 (0.8)		1 (1.6)		25–29.9 versus ≥30		0.144

*Significant at the level of 0.25 for univariate analysis and included in multivariate analysis.
**Significant at the level of 0.05 for multivariate analysis.

Table 2: Analysis of factors associated with major complications following liver resection in 504 patients.

$N = 504$	No complication ($n = 410$)	Major complication ($n = 94$)	Univariate		Multivariate	
			P value		Odds ratio (95% CI)	P value
Median age (range)	64 (21–90)	67 (32–88)	0.015*		1.03 (0.99–1.07)	0.004**
Gender (%)						
Male	211 (51.5)	67 (71.3)	0.001*		2.36 (1.34–4.17)	0.028**
Female	199 (48.5)	27 (28.7)				
Pathology (%)						
Benign	34 (8.3)	6 (6.4)				
Primary	83 (20.2)	23 (24.5)	0.622			
Secondary	293 (71.5)	65 (69.1)	0.308			
Liver-directed chemotherapy (%)	130 (31.7)	33 (35.1)	0.608			
Preexisting chronic liver disease (%)	10 (2.4)	1 (1.1)	0.666			
Preoperative jaundice (≥50 micromoles/L) (%)	6 (1.5)	3 (3.2)	0.266			
Hypoalbuminaemia (<35 g/L) (%)	9 (2.2)	8 (8.5)	0.004*		2.97 (1.01–8.74)	0.047**
Raised preoperative alkaline phosphatase (%)	95 (23.2)	24 (25.5)	0.721			
Raised preoperative transaminase (%)	74 (18.0)	21 (22.3)	0.320			
Preoperative glomerular filtration rate (%)						
≤90 mL/min	274 (66.8)	63 (67.0)	0.892			
Median preoperative haemoglobin (g/dL) (range)	13 (9–17)	13 (9–16)	0.025*			0.439
Median preoperative white cell count (/L) (range)	7 (3–17)	7 (3–25)	0.422			
Diabetic status (%)						
Nondiabetic	370 (90.2)	78 (83.0)				0.912
Non-insulin dependent (versus nondiabetic)	32 (7.8)	9 (9.6)	0.014*			
Insulin dependent diabetes (versus non-insulin dependent and nondiabetics)	8 (2.0)	7 (7.4)			3.86 (1.17–12.75)	0.028**
Body mass index (kg/m^2) (%)						
<25	139 (33.9)	28 (29.8)				
25–30	167 (40.7)	42 (44.7)	0.697			
>30	99 (24.1)	24 (25.5)				
American Association of Anesthesiologists (ASA) grade (%)						
1 versus 2						
1	46 (11.2)	6 (6.4)				0.611
2	266 (64.9)	58 (61.7)	0.198*			
2 versus 3 and 4						
3	95 (23.2)	30 (31.9)				0.783
4	2 (0.5)	0				
Median P-POSSUM physiologic score (range)	16 (12–32)	18 (12–30)	0.003*			0.764

Table 2: Continued.

$N = 504$	No complication ($n = 410$)	Major complication ($n = 94$)	Univariate P value	Multivariate Odds ratio (95% CI)	Multivariate P value
Operative approach (%)					
Laparoscopic	46 (11.2)	4 (4.3)	0.065*		0.812
Open	364 (88.8)	90 (95.7)			
Radiofrequency ablation included (%)	18 (4.4)	5 (5.3)	0.698		
Wedge resection included (%)	181 (44.1)	22 (23.4)	<0.001*		0.353
Bile-duct reconstruction (%)	34 (8.3)	12 (12.8)	0.246*		0.585
Synchronous bowel procedure (%)	13 (3.2)	10 (10.6)	0.003*	5.99 (2.25–15.96)	<0.001**
Median number of segments resected (range)	3 (1–6)	4 (1–6)	<0.001	1.51 (1.26–1.80)	<0.001**
Repeat operation (%)	31 (7.6)	6 (6.4)	0.861		
Intraoperative blood loss (%)					
<500 mL	218 (53.2)	29 (30.9)	<0.001		0.463
≥500 mL	188 (45.9)	65 (69.1)			
Blood transfusion required (%)	65 (15.9)	41 (43.6)	<0.001	2.48 (1.44–4.30)	0.001**
Steatosis (%)					
<33%	308 (75.1)	70 (74.5)	1.000		
≥33%	50 (12.2)	11 (11.7)			

*Significant at the level of 0.25 for univariate analysis and included in multivariate analysis.
**Significant at the level of 0.05 for multivariate analysis.

Table 3: Postoperative complications, 90-day mortality, and diabetic status in 504 patients undergoing liver resection (patients may have had more than one complication).

$N = 504$	All patients ($n = 504$)	Nondiabetic ($n = 448$)	Non-insulin dependent diabetes ($n = 41$)	Insulin dependent diabetes ($n = 15$)	P value Nondiabetic versus non-insulin dependent diabetic	P value Nondiabetic versus insulin dependent diabetic
	Count (%)	Count (%)	Count (%)	Count (%)		
Any major complication	94 (18.7)	78 (17.4)	9 (21.9)	7 (46.6)	0.521	0.010
90-day mortality (Grade V)						
Liver failure	9 (1.8)	5 (1.1)	3	1	0.023*	0.180
Sepsis	4 (0.8)	3 (0.7)	1	0	0.296	1.000
Malignancy	4 (0.8)	3 (0.7)	0	1	1.000	0.124
Pulmonary embolus	1 (0.2)	1 (0.2)	0	0	1.000	1.000
Anastomotic leak	1 (0.2)	1 (0.2)	0	0	1.000	1.000
Peptic ulcer	1 (0.2)	1 (0.2)	0	0	1.000	1.000
Strangulated hernia	1 (0.2)	1 (0.2)	0	0	1.000	1.000
Peritonitis	1 (0.2)	1 (0.2)	0	0	1.000	1.000
Heart failure	1 (0.2)	1 (0.2)	0	0	1.000	1.000
Total	**23 (4.6)**	**17 (3.8)**	**4**	**2**	**0.089**	**0.122**
Grade IV complications						
Posthepatectomy liver failure (PHLF)	34 (6.7)	30 (6.7)	4	0	0.515	0.613
Renal dysfunction	31 (6.2)	24 (5.4)	4	3	0.280	0.050
Respiratory failure requiring intensive care	2 (0.4)	2 (0.4)	0	0	1.000	1.000
Total	**67 (13.3)**	**56 (12.5)**	**8**	**3**	**0.224**	**0.421**
Grade III complications						
Bile leak						
Drain	12 (2.4)	11 (2.5)	0	1	0.611	0.330
ERCP	11 (2.2)	10 (2.2)	1	0	1.000	1.000
Relaparotomy/relaparoscopy						
Washout	3 (0.6)	1 (0.2)	1	1	0.161	0.064
Adhesiolysis	2 (0.4)	2 (0.4)	0	0	1.000	1.000
Defunction for anastomotic leak	1 (0.2)	0	1	0	0.084	1.000
Small bowel leak	1 (0.2)	1 (0.2)	0	0	1.000	1.000
Drainage						
Liver abscess	1 (0.2)	1 (0.2)	0	0	1.000	1.000
Pleural effusion	1 (0.2)	0	0	1	1.000	0.032
Pneumothorax	1 (0.2)	1 (0.2)	0	0	1.000	1.000
Subphrenic collection	2 (0.4)	2 (0.4)	0	0	1.000	1.000
Total	**35 (6.9)**	**29 (6.5)**	**3**	**3**	**0.743**	**0.077**

($P = 0.388$). Similarly there was no significant difference in the proportion of patients with steatosis ≥33% between patients who did (4/22, 15.6%) or did not (29/243, 11.9%) develop PHLF ($P = 0.495$).

4. Discussion

The principal finding of this study is that although diabetes mellitus and higher BMI are risk factors for steatosis in patients undergoing liver resection, the majority of cases of steatosis occur in nondiabetic patients with mildly elevated BMI (25–30). Secondly, steatosis and elevated BMI are not associated with major complications after liver resection, and diabetes is a risk factor for these complications only if patients are insulin dependent. Other predictors of major complications are older age, male gender, preoperative hypoalbuminaemia, synchronous bowel procedures, number of segments resected, and requirement for blood transfusion.

The 90-day mortality (4.6%) and morbidity (14.7%) rate are similar to published series [4, 18, 38], although other series have included minor (Grade I and II) complications [39–41]. Composite outcomes similar to the one used in this study have been used previously in studies evaluating outcomes following gastrointestinal surgery [42, 43]. The present study confirms the association between hepatic steatosis and BMI [44]. Whilst the rate of moderate/severe steatosis was greatest in overweight diabetic patients (38.5%), it also occurred in patients of normal weight without diabetes (4.4%). This suggests that other risk factors may be involved in the aetiology of the disease. Undernutrition [17], impaired glucose tolerance [45], and genetic factors [46] have also been implicated in the development of NAFLD. Alcohol consumption is an unlikely cause of steatosis in this series as all patients are asked to abstain from alcohol consumption prior to surgery, although compliance with this instruction has not been assessed.

Elevated transaminase levels are associated with hepatic steatosis, but the sensitivity of abnormal transaminases in detecting moderate or severe NAFLD is poor, as 70% of these patients had normal transaminase levels. This is in keeping with other studies [47]. Interestingly, raised preoperative alkaline phosphatase concentration was associated with decreased incidence of steatosis. Elevated alkaline phosphatase may be found in cases of biliary obstruction, and of the 119 patients with this finding 16.8% had cholangiocarcinomas compared to only 2.9% of the 380 patients with normal alkaline phosphatase. This group is more likely to be systemically unwell as a consequence of biliary obstruction and to have suffered a period of anorexia and weight loss, which may affect the degree of hepatic steatosis.

Preoperative chemotherapy was not shown to be associated with steatosis. Studies have shown an association between steatohepatitis and irinotecan therapy [18], which was rarely used in this series. In addition the policy in this unit is to use only four cycles of chemotherapy and to allow a period of recovery before undertaking liver resection, to allow resolution of hepatotoxicity.

Previous studies have shown that steatosis increases the risk of PHLF [8, 21]. The rate of PHLF in this series was low (6.7%) and occurred in 6.6% patients with moderate/severe steatosis and 6.1% of the patients with none/mild steatosis. The majority of cases of PHLF followed major liver resection (29/34). It is possible that there is an independent association between steatosis and PHLF, which is not revealed in this study which uses a composite outcome including other complications in the multivariate analysis. Steatosis may be a risk factor for liver failure in patients undergoing extended hepatectomy, although not in major hepatectomy in this series, where the risk of this complication is greatest. Previous studies have recommended liver biopsy to investigate the presence of steatosis prior to resection [48, 49]. The current study suggests that the risk of this investigation is not justified due to the lack of effect of steatosis on outcome.

The rate of bile leak requiring intervention (4.6%) was not affected by the degree of hepatic steatosis suggesting that hepatic steatosis does not make parenchymal division more difficult to perform.

Elevated BMI was not associated with major complications in this series, although it may be associated with more minor complications such as wound infection which has not been explored in this study.

Diabetes was an independent risk factor for complications after liver surgery which confirms the findings of previous studies [5, 50–52], although identification of insulin dependence as the major risk factor is a novel finding. Whilst there was no significant difference in the risk of major complications between nondiabetic patients and those with non-insulin dependent diabetes, the risk of complications was more than trebled in those with insulin dependent diabetes. This finding reflects the multisystem nature of diabetic end-organ damage. Diabetic nephropathy is a major cause of renal dysfunction [53] and was the most common complication in patients with IDDM. Renal dysfunction was also twice as common amongst patients with IDDM compared to those with NIDDM.

Older age, male gender, preoperative hypoalbuminaemia, number of liver segments resected, and requirement for blood transfusion have all been previously identified as risk factors for postoperative complications [38]. The finding that performing synchronous bowel procedures is associated with worse outcome is similar to that of a previous study which found that the risk of a major complication was 20.4% after a synchronous colonic resection compared to 14.9% after a liver-only resection [54]. Although a recent systematic review suggested no difference in terms of overall morbidity or mortality between synchronous and staged resections [55] the results of the present study reveal the risk of developing a major complication after a synchronous bowel procedure was almost six times that of a liver-only resection. It should also be noted that the synchronous procedures included a gastric resection and Whipple's procedure which may pose different risks to colonic resections. Most of the increased risk in this context relates to leaks from enteric anastomoses.

5. Conclusions

The results of this study allow clinicians to advise patients regarding the risks of liver resection and to place them

in context. In particular, liver surgery in the presence of steatosis, elevated BMI, and NIDDM does not lead to greatly increased operative risk. While insulin dependence is a significant risk factor for complications after liver surgery, the major risk factors in this series related to technical details of the operation, particularly the performance of simultaneous bowel procedures.

Conflict of Interests

The authors declare no conflict of interests regarding the publication of this paper.

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Serum arterial lactate concentration predicts mortality and organ dysfunction following liver resection

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Abstract

Background: The aim of this study was to determine if the post-operative serum arterial lactate concentration is associated with mortality, length of hospital stay or complications following hepatic resection.

Methods: Serum lactate concentration was recorded at the end of liver resection in a consecutive series of 488 patients over a seven-year period. Liver function, coagulation and electrolyte tests were performed post-operatively. Renal dysfunction was defined as a creatinine rise of >1.5x the pre-operative value.

Results: The median lactate was 2.8 mmol/L (0.6 to 16 mmol/L) and was elevated (≥2 mmol/L) in 72% of patients. The lactate concentration was associated with peak post-operative bilirubin, prothrombin time, renal dysfunction, length of hospital stay and 90-day mortality ($P < 0.001$). The 90-day mortality in patients with a post-operative lactate ≥6 mmol/L was 28% compared to 0.7% in those with lactate ≤2 mmol/L. Pre-operative diabetes, number of segments resected, the surgeon's assessment of liver parenchyma, blood loss and transfusion were independently associated with lactate concentration.

Conclusions: Initial post-operative lactate concentration is a useful predictor of outcome following hepatic resection. Patients with normal post-operative lactate are unlikely to suffer significant hepatic or renal dysfunction and may not require intensive monitoring or critical care.

Keywords: Liver, Hepatectomy, Post-operative care

Background

Despite advances in both operative technique and peri-operative care, liver resection is associated with post-operative mortality rates of 0% to 22% (median 3.7%) [1] and morbidity rates of 12.5% to 66% including liver dysfunction [2,3], renal dysfunction [4] and bile leak [5,6]. Factors associated with peri-operative complications and death include patient age [7,8] and gender [9,10], hospital annual number of liver resections undertaken [9,11], pathologic origin of liver tumour [9,11], pre-operative liver and renal dysfunction [8,10], diabetes [12,13], chronic liver disease [7,9], and the peripheral neutrophil to lymphocyte ratio (NLR) [14]. Operative factors associated with outcome include blood loss [8,10] and transfusion [15,16], extent of liver resection [15,17], duration of surgery [18], simultaneous extrahepatic procedures [15,19], and the use of the Pringle manoeuvre [16,20].

Therefore, many factors affect outcome after liver surgery which have not been incorporated into a single scoring system. The American Society of Anesthesiologists (ASA) grade and Portsmouth Physiologic and Operative Severity Score for the enUmeration of Mortality and morbidity (P-POSSUM) scores are used in the risk prediction of many types of surgery [21,22] including liver surgery [23]. However, these scores may not be applicable to the unique stresses of liver resection. One of the main reported causes of mortality following liver resection is post-hepatectomy liver failure (PHLF) [24]. Although

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the '50-50 criteria' of serum bilirubin of >50 μmol/L and prothrombin index (laboratory's calculated mean normal prothrombin time (PT) divided by the patient's observed PT) of <50% measured on the fifth post-operative day have been shown to be associated with death due to PHLF [2], an earlier prediction system may be clinically more useful in guiding therapy. Furthermore, failure of multiple organ systems may contribute to death following liver resection and there is a need for a global peri-operative measure to predict the risk of developing significant post-operative morbidity and death.

Lactic acid is a by-product of anaerobic metabolism that is subsequently metabolised in the liver during gluconeogenesis [25]. Hyperlactataemia has been shown to be associated with increased mortality and morbidity in a critical care setting [26,27], in patients with liver failure [28], sepsis [29] and following trauma [30]. Similar relationships have been shown in the post-operative setting following pancreatic resection [31] and other major abdominal surgery [32], cardiac surgery [33] and after hepatic transplantation [34].

The primary aim of this study was to determine if the first post-operative arterial lactate concentration ('initial lactate') is associated with adverse outcomes following liver resection including 90-day mortality, length of hospital stay (LOS), and renal and hepatic dysfunction. The secondary aim was to determine which pre- and intra-operative risk factors are associated with initial lactate concentration following liver resection.

Methods

This study was a retrospective analysis of a prospectively maintained database of all patients undergoing liver resection since July 2005. Routine patient characteristics, laboratory data and intra-operative details were retrieved. Pre-operative liver-directed chemotherapy was administered to selected patients following discussion at a regional multidisciplinary team meeting. A period of recovery of at least six weeks was allowed following cessation of chemotherapy before undertaking surgery. The P-POSSUM scoring system was used to calculate the physiological score [21]. Prior to resection, the operating surgeon makes a visual assessment of the condition of the liver parenchyma and records this as normal or abnormal. Liver resections were performed using standard techniques with a Cavitron Ultrasonic Surgical Aspirator™ (CUSA; Tyco Healthcare, Mansfield, MA, USA) dissector. Hepatic inflow occlusion was used in a minority of cases where there was excessive blood loss. Anaesthetic techniques include the routine use of invasive arterial blood pressure monitoring, central venous pressure monitoring (CVP) (using a target CVP of <5 cm H20) and epidural anaesthesia. Liver resections were defined according to the Brisbane classification [35] and the number of removed segments recorded. Intravenous fluid replacement was minimised during the resection phase to decrease venous pressure. After removal of the surgical specimen, a pause in surgical activity is routinely planned to allow haemostasis and intravenous volume replacement with 0.9% saline or Hartmann's solution at the anaesthetist's discretion. Patients are usually returned to the High Dependency Unit (HDU) after surgery with full invasive monitoring, except for minor resections in fit patients who are returned to the general ward.

The serum lactate was recorded from an arterial blood sample taken immediately prior to abdominal closure or immediately on arrival in the HDU. The arterial lactate in the normal population is below 1.6 mmol/L whereas in a critical care setting <2 mmol/L is more commonly accepted in acutely stressed patients [36].

Serum biochemistry tests and coagulation assays were performed on all patients in the first 24 hours post-operatively and the tests repeated according to clinical course. The peak measurement of bilirubin and PT were recorded and used for analysis. A PT index of <50% corresponds to a PT >24 s. Similarly peak post-operative creatinine levels were obtained and renal dysfunction was defined according to the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) criteria [37]. Renal dysfunction in categorical analyses was defined as any increase in serum creatinine of ≥1.5-fold from the pre-operative baseline. The length of hospital stay was measured from day of surgery to day of discharge and was expressed as a natural logarithm. Ninety-day mortality was recorded.

The association between initial serum lactate concentration and continuous outcomes was investigated using a multiple linear regression model as well as Spearman's rank correlation. To overcome increasing variance with the mean a natural log transformation was used. Binary variables were investigated using univariate regression. Potential associations between initial lactate concentration and pre- and intra-operative factors were tested using univariate regression or chi-square test at the level of $P < 0.25$ [38], as appropriate. Significant variables in the univariate analysis were included in the multivariate regression model and were considered to be significant if $P < 0.05$. All analyses were carried out using the statistical package R 2.1.14 [39].

Confirmation was obtained from the South West Health Research Authority that under the harmonised Guidance Approval for Research Ethics Committees (REC), REC review was not required because patient data was collected in the course of their normal hospital care and was anonymised for research purposes. No patient consent was required for this study.

Results

In the study period 501 patients underwent liver resection for whom an initial lactate measurement was available in

Table 1 Pre-operative and intra-operative characteristics of 488 patients undergoing liver resection

n = 488			Median (range)	Count (%)
Age (years)			65 (21–90)	
Gender	Female			216 (44.3)
	Male			272 (55.7)
Pathology of resected specimen	Benign			40 (8.2)
	Primary	Hepatocellular carcinoma		30 (6.1)
		Cholangiocarcinoma		36 (7.4)
		Other		35 (7.2)
	Secondary	Colorectal metastases		291 (59.6)
		Other		56 (11.5)
Pre-operative liver-directed chemotherapy	Yes			173 (35.5)
	No			315 (64.5)
Body mass index			26 (16–54)	
P-POSSUM physiologic score			16 (12–32)	
ASA grade	1			49 (10.1)
	2			315 (64.7)
	3			121 (24.8)
	4			2 (0.4)
Pre-operative diabetes	Yes			55 (11.3)
	No			433 (88.7)
Pre-operative bilirubin (μmol/L)			9 (2–162)	
Pre-operative alkaline phosphatase (U/L)			95 (34–1190)	
Pre-operative albumin (g/L)			44 (10–53)	
Pre-operative creatinine (μmol/L)			78 (40–430)	
Pre-operative glomerular filtration rate (ml/min)	≤90			158 (33.2)
	>90			318 (66.8)
Neutrophil to lymphocyte ratio (NLR)			2.47(0.3-17.3)	
Operation number	1st			453 (92.8)
	2nd			30 (6.1)
	3rd			5 (1.0)
Surgeons assessment of liver parenchyma	Normal			314 (65.3)
	Abnormal			167 (34.7)
Surgical approach	Open			440 (90.2)
	Laparoscopic			48 (9.8)
Radiofrequency ablation (RFA) included	Yes			22 (4.5)
	No			466 (95.5)
Operation	Right hemihepatectomy			142 (29.1)
	Extended right hemihepatectomy			65 (13.3)
	Left hemihepatectomy			55 (11.3)
	Extended left hemihepatectomy			24 (4.9)
	Left lateral sectorectomy			45 (9.2)
	Wedge resection only			127 (26.0)
	Other			30 (6.1)

Table 1 Pre-operative and intra-operative characteristics of 488 patients undergoing liver resection *(Continued)*

Wedge resection included	Yes		182 (37.3)
	No		306 (62.7)
Bile duct reconstruction included	Yes		43 (8.8)
	No		445 (91.2)
Synchronous bowel procedure	Yes		22 (4.5)
	No		466 (95.5)
Curative intent	Yes		442 (90.6)
	No		46 (9.4)
Number of segments resected		4 (1–6)	
Estimated blood loss	<100 ml		2 (0.4)
	101-500 ml		240 (49.7)
	501-1000 ml		167 (34.6)
	>1000 ml		74 (15.3)
Units of red cells transfused		0 (0–26)	

488. The indications for surgery, pre-operative and operative details are shown in Table 1. Results of blood tests are shown in Table 2 and the main post-operative outcome measures are summarised in Table 3. The median number of biochemistry tests performed per patient in the first five post-operative days was 4 (0 to 6) and coagulation assays was 3 (0 to 6). It was not necessary to administer clotting factors to any surviving patients between postoperative days 1 to 5. Peak abnormalities in PT and bilirubin usually occurred early in the post-operative course and tended to improve over five days (Table 2). Post-operatively, 118 patients (24.1%) had a serum bilirubin ≥50 μmol/L. Minor abnormalities in PT were commonly noted, though only 15 patients (3.1%) developed a PT >24 s. Although a small number of patients remained jaundiced at the time of discharge, only one patient fulfilled the '50-50 criteria' at day five. The median length of hospital stay was seven days (range 2 to 78) with 90% of patients having a LOS between two and 15 days. Twelve patients (2.5%) died within 30 days of surgery and 23 died within 90 days of surgery (4.7%). The most common cause of death was liver failure, which occurred in 11 of 23 patients. Four patients died from ongoing malignancy (of whom three had undergone non-curative resections) and two patients died from sepsis without evidence of liver failure. The remaining deaths were attributed to pulmonary embolus, heart failure, anastomotic leak following colonic resection, bleeding peptic ulcer, strangulated hernia and peritonitis.

The median initial lactate concentration was 2.8 mmol/L (inter-quartile range = 1.9 to 3.9) and 350 patients (72%) had an elevated serum lactate concentration (≥2 mmol/L) (Figure 1). There was no difference in the lactate concentration taken prior to abdominal closure (n = 380, median 2.8 mmol/L, range 0.6 to 16.0) or immediately on arrival in the HDU (n = 108, median 2.8 mmol/L, range 0.6 to 14.0). The initial lactate concentration was noted to be associated with all recorded outcome measures (Table 4). Although major abnormalities of serum bilirubin and PT were rare in our series there was a weak correlation with initial lactate for both bilirubin (coefficient 0.41, $P < 0.001$) and PT (coefficient 0.37, $P < 0.001$), which was stronger for bilirubin. Similarly, there was a weak correlation with length of hospital stay (coefficient 0.28, $P < 0.001$). Of note the values for length of hospital stay include only survivors, and therefore exclude some patients who are likely to have high post-operative lactate levels. Renal dysfunction after liver resection was rare in this series (7.0%) but there was a correlation with lactate concentration (Table 4). Three of 137 patients (2.2%) with an initial lactate concentration less than 2 mmol/L who

Table 2 Post-operative blood tests for 488 patients undergoing liver resection

n = 488		POD 0	POD 1	POD 2	POD 3	POD 4	POD 5
Bilirubin	Tested (%)	393 (81)	385 (79)	324 (66)	255 (52)	213 (44)	200 (41)
	Median (range)	21 (5–170)	27 (6–211)	21 (4–195)	19 (3–167)	18 (4–179)	19 (1–186)
Prothrombin time	Tested (%)	387 (79)	317 (65)	233 (48)	170 (35)	135 (28)	107 (22)
	Median (range)	16.3 (12.2-32.4)	18.0 (12–200)	18.0 (12.6-39.4)	16.1 (11.2-37.2)	15.3 (11.6-30.6)	15.4 (12.0-26.4)
Creatinine	Tested (%)	425 (87)	458 (94)	374 (77)	288 (59)	241 (49)	226 (46)
	Median (range)	70 (30–319)	70.5 (29–377)	64.5 (26–686)	60.5 (28–518)	59 (25–611)	60 (26–292)

Table 3 Post-operative outcomes for 488 patients undergoing liver resection

n = 488	Median (range)	Count (%)
Peak bilirubin (μmol/L)	29 (4–445)	
Peak prothrombin time (s)	17.6 (12.4-200)	
Length of stay (days)	7 (2–78)	
Renal dysfunction	None	450 (92.2)
	Risk (>1.5x pre-operative creatinine)	17 (3.5)
	Injury (>2x pre-operative creatinine)	12 (2.5)
	Failure (>3x pre-operative creatinine)	5 (1.0)
90-day mortality		23 (4.7)

had creatinine measured developed renal dysfunction (negative predictive value (NPV) = 0.98) compared to 8 of 29 (27.5%) patients with an initial lactate greater than 6 mmol/L (positive predictive value (PPV) = 0.28) (P = < 0.001) (Figure 2). In 322 patients with a lactate concentration ≥2 and <6 mmol/L 23 developed renal dysfunction (7.1%).

Similarly, there was a correlation between mortality in the 90-day period following liver resection and initial lactate concentration (Table 4). One of 138 patients (0.7%) with an initial lactate concentration <2 mmol/L died within this period, due to an anastomotic leak following colonic resection (NPV = 0.99), compared to eight of 29 patients with initial lactate ≥6 mmol/L (PPV = 0.28) (P = < 0.001) (Figure 3). The deaths in patients with lactate ≥6 mmol/L were due to liver failure in four patients, sepsis without liver failure in two patients, cardiac failure in one patient and ongoing malignancy in the other. Of the remaining 322 patients with lactate concentration ≥2 and <6 mmol/L there were 14 deaths within 90 days of surgery (4.3%).

Comparison of patients with initial lactate concentrations <2 mmol/L and ≥6 mmol/L revealed there were significantly more major resections performed (P < 0.001) and more patients with pre-operative diabetes (P < 0.001) in patients with a lactate concentration ≥6 mmol/L (Table 5). There was no significant difference in the use of pre-operative chemotherapy between these two groups (P = 0.351). The proportion of patients with both renal dysfunction and who died within 90 days was significantly higher in those with lactate concentrations ≥6 mmol/L (P < 0.001).

Regression analysis revealed that a pre-operative diagnosis of diabetes mellitus, the number of liver segments resected, the operating surgeon's assessment of the health of the liver parenchyma, the operative blood loss and number of units of red cells transfused were all independently associated with initial lactate concentration at closure (Table 6). The only pre-operative factor associated with the post-operative lactate concentration was the presence of diabetes. On average, this increased the post-operative lactate concentration at any level by 20% compared to non-diabetics.

Discussion

The principal findings of this study are that higher initial serum lactate concentration after liver resection is

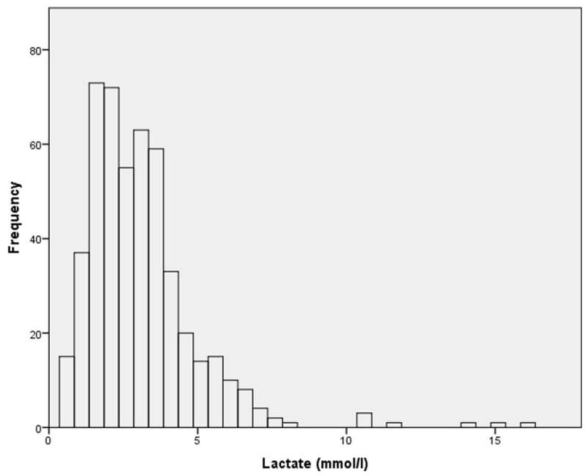

Figure 1 Distribution of arterial lactate concentration in 488 patients at the end of liver resection.

Table 4 Univariate analysis of the association between lactate and postoperative outcomes for 488 patients undergoing liver resection

n = 488	Co-efficient ± SD	*P* value
Peak bilirubin	0.146 ± 0.017	<0.001*
Peak prothrombin time	0.055 ± 0.002	<0.001*
Length of stay	0.046 ± 0.006	<0.001*
Renal dysfunction	0.324 ± 0.072	<0.001*
90-day mortality	0.373 ± 0.079	<0.001*

*Significant at level of P <0.05.

associated with an increased risk of mortality and renal and liver dysfunction. Both the 90-day mortality rate and the rate of renal dysfunction in patients with initial lactate concentrations greater than 6 mmol/L were 28% compared to those patients with initial lactate concentrations less than 2 mmol/L where they were 0.7% and 2.2% respectively. Similarly, higher lactate concentration was associated with higher post-operative peaks in serum bilirubin concentration and PT, as well longer lengths of hospital stay.

These findings support and extend those of an earlier study [40] by demonstrating the association of post-operative lactate with renal and hepatic dysfunction and length of hospital stay in addition to mortality. Pre-operative diabetes mellitus, the surgeon's assessment of the liver at laparotomy, the extent of liver resection, blood loss and the number of units of blood transfused are also shown to be associated with post-operative serum lactate concentration.

During cellular hypoxia pyruvate is diverted from the citric acid cycle and converted to lactate, reducing the amount of adenosine triphosphate (ATP) generated. This occurs in all metabolically active tissues including muscle, gut, liver, brain, erythrocytes and skin [41-43] and is exacerbated by intra-operative stresses including blood loss [42], endogenous release of stress hormones [44] and administration of pressor agents [45]. Liver ischaemia induced by handling of the liver during surgery and temporary inflow occlusion has been shown to lead to a rise in lactate [46]. Serum lactate can also be increased by transfusion of stored blood, which contains a higher concentration of lactate than fresh blood depending on length of storage [47]. Administration of Hartmann's solution has been shown to have a small effect on serum lactate concentration [48]. A potential weakness of this study is that details of pressor agents were not recorded, which could affect the lactate concentration. Similarly precise details regarding intravenous fluid type and volume of fluid (colloid and crystalloid) were not recorded.

In addition to being a potential source of lactate the liver is the principle location of lactate metabolism, where it is converted back to glycogen, accounting for 70% of

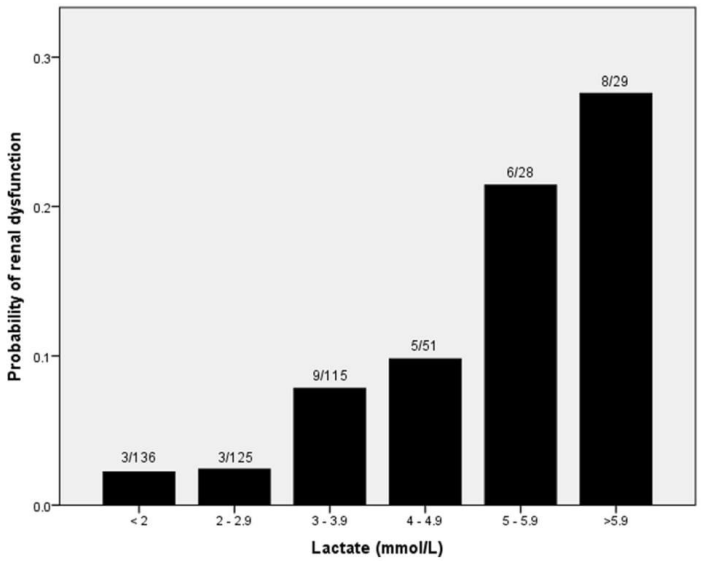

Figure 2 Probability of renal dysfunction after liver resection according to lactate concentration in 484 patients.

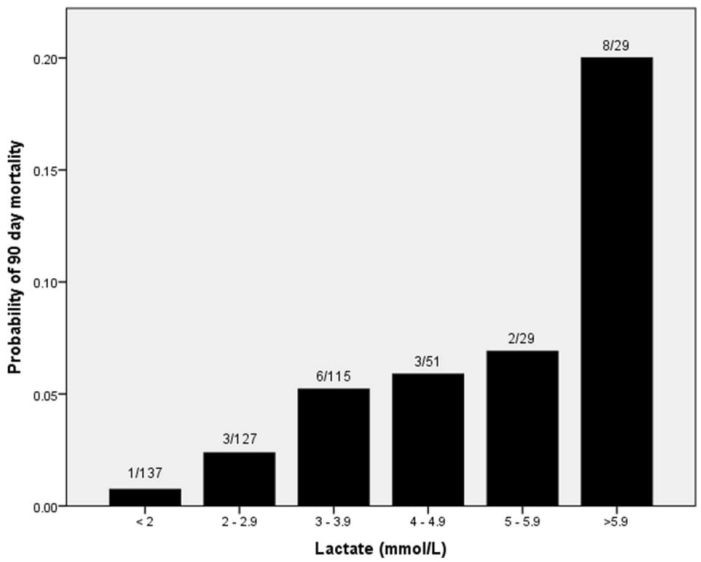

Figure 3 Probability of 90-day mortality after liver resection according to lactate concentration in 488 patients.

whole body lactate clearance [42]. No change in lactate metabolism has been demonstrated following recovery from partial hepatectomy in either rats [49] or humans [25], implying that the liver has a large functional reserve under physiological conditions of lactate production. However, the effects of intra-operative stress on hepatic glucose homeostasis have not been assessed, particularly when in combination with an extended hepatectomy. It is possible that inflow occlusion during resection and intra-operative handling of the liver lead to a temporary impairment of the ability of the liver to metabolise lactate. The finding of an association between the number of liver segments resected and the initial post-operative lactate supports this hypothesis. Diabetes is also known to be associated with impaired lactate metabolism via gluconeogenesis [42] and may account for the strong association with post-operative lactate in this series. Furthermore, the use of metformin in non-insulin-dependent diabetes has also been shown to increase lactate concentration [50]. The rise in serum lactate at the end of liver resection therefore may be due to a failure of lactate metabolism in addition to increased production during surgery.

Table 5 Distribution of risk factors and outcomes in 138 patients with lactate <2 mmol/L and 29 patients with lactate ≥6 mmol/L undergoing liver resection

Lactate	<2 mmol/L (n = 138)	≥6 mmol/L (n = 29)	*P* value
Major resection (%)	26 (18.8)	26 (89.7)	<0.001*
Pre-operative chemotherapy (%)	38 (27.5)	5 (17.2)	0.351
Pre-operative diabetes (%)	6 (4.3)	8 (27.6)	<0.001*
Post-operative renal dysfunction (%)	3 (2.2)	8 (27.6)	<0.001*
90-day mortality (%)	1 (0.7)	8 (27.6)	<0.001*

*Significant at level of P <0.05.

Significantly, the use of pre-operative chemotherapy was not shown to be associated with elevation of post-operative lactate. This may be due to a policy of allowing a period of recovery after completion of pre-operative chemotherapy before undertaking surgery. Interestingly, the operating surgeon's assessment of the liver parenchyma was associated with the post-operative lactate concentration. This finding suggests that patient co-morbidity was a more common cause of abnormal liver parenchyma than the use of liver-directed chemotherapy.

An important observation of this study is the relative rarity of major hepatic dysfunction following liver resection in this series with only one patient fulfilling the '50-50' criteria [2], who subsequently recovered. Despite the infrequency of major disturbances of post-operative bilirubin and PT, there was an independent association with increasing concentration of post-operative lactate, demonstrating that even a minor degree of liver injury can lead to impaired lactate clearance or increase its production.

Renal dysfunction was also rare in this series, affecting 34 patients (7%) compared to 15% in a similar series

Table 6 Univariate and multivariate analysis of pre- and intra-operative factors associated with serum lactate concentration following liver resection in 488 patients

N = 488		Univariate analysis	Multivariate analysis	
Factor		***P* value**	**Co-ef +/− SD**	***P* value**
Age		0.246*		0.925
Gender		0.012*		0.129
Pathology	Benign vs. Primary	0.442		0.144
	Primary vs. Secondary	0.226*		0.878
Liver-directed chemotherapy		0.129*		0.219
Open or laparoscopic resection		0.009*		0.611
Radiofrequency ablation		0.191*		0.402
Wedge resection included		<0.001*		0.086
Bile duct reconstruction		0.004*		0.651
Number of segments resected		<0.001*	0.143 ± 0.012	<0.001†
Synchronous bowel procedure		0.516		
Surgeon's assessment of liver		<0.001*	0.185 ± 0.042	<0.001†
Redo operation	1st vs. 2nd resection	0.268		
	2nd vs. 3rd resection	0.654		
Pre-operative diabetes		<0.001*	0.204 ± 0.064	0.002†
Body mass index		0.06*		0.905
ASA grade	1 vs. 2	0.014*		0.824
	2 vs. 3	0.709		0.872
P-POSSUM physiologic score		0.054*		0.221
Hepatic fibrosis/cirrhosis		0.667		
Pre-operative bilirubin		0.320		
Pre-operative haemoglobin		0.633		
Neutrophil:lymphocyte ratio		0.400		
Pre-operative albumin		0.399		
Pre-operative alkaline phosphatase		0.014*		0.775
Pre-operative creatinine		0.392		
Pre-operative glomerular filtration rate (GFR) >90 ml/min		0.042*		0.054
Blood loss (ml)	<500 vs. 500-999	<0.001*	0.131 ± 0.038	0.013†
	500-999 vs. >1000	0.435		0.884
Units of red cells transfused		<0.001*	0.043 ± 0.011	<0.001†

*Significant at the level of 0.25 for univariate analysis and included in multivariate analysis; †significant at the level of 0.05 for multivariate analysis.

[51]. The risk factors for post-operative renal dysfunction are likely to be similar to those in other forms of abdominal surgery, including blood loss and sepsis, which are also initiating factors for anaerobic metabolism and lactate production. This supports the value of initial lactate as an early predictor of renal dysfunction. Of note, the risk of renal dysfunction appeared to rise more rapidly when the post-operative lactate rose above 5 mmol/L (Figure 2). This suggests that the kidneys are able to tolerate a degree of oxidative stress to a threshold level beyond which the risk of damage rises rapidly.

There was a weak association between initial lactate concentration and length of hospital stay in the study (Table 4). However, this may also be affected by other factors such as post-operative complications, particularly bile leaks, and degree of social support.

The strongest association demonstrated was between lactate concentration and the risk of mortality. In a similar manner to renal dysfunction, there seems to be a threshold level of post-operative lactate of approximately 6 mmol/l above which the risk of 90-day mortality rises rapidly (Figure 3). Organ dysfunction was a major contributor to mortality in the series and initial lactate concentration is a valuable global marker of poor organ function in the early post-operative period, including cardiovascular, renal and hepatic dysfunction.

Conclusions

These findings are of value in clinical practice as it may be possible to use the initial post-operative lactate concentration to determine the patient pathway in the early post-operative period. Patients with an initial post-operative lactate of less than 2 mmol/L have low rates of mortality and organ dysfunction and we are currently evaluating this criterion as a determinant of the need for post-operative critical care. In addition the correlation of post-operative lactate with subsequent organ dysfunction and mortality may allow its use as a single measure of the impact of innovations in operative technique or peri-operative care.

Abbreviations

ASA: American society of anesthesiologists; ATP: Adenosine triphosphate; CUSA: Cavitron ultrasonic surgical aspirator; CVP: Central venous pressure; HDU: High dependency unit; LOS: Length of stay; NLR: Neutrophil to lymphocyte ratio; NPV: Negative predictive value; PHLF: Post-hepatectomy liver failure; P-POSSUM: Portsmouth physiologic and operative severity score for the enUmeration of mortality and morbidity; PPV: Predictive value; PT: Prothrombin time; REC: Research ethics committee; RIFLE: Risk, injury, failure, loss, and end-stage kidney disease.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MW and TS designed the study, collected data, analysed the data and drafted the manuscript. GS participated in the design of the study and performed the statistical analysis. TW, DB, PE, IA, SA and MB participated in the design of the study, collected data and drafted the manuscript. DS conceived the study, supervised its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Authors' information

M.G. Wiggans and T. Starkie: joint first authors.

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Research Article

Renal Dysfunction Is an Independent Risk Factor for Mortality after Liver Resection and the Main Determinant of Outcome in Posthepatectomy Liver Failure

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Introduction. The aim of this study was to assess the interaction of liver and renal dysfunction as risk factors for mortality after liver resection. *Materials and Methods*. A retrospective analysis of 501 patients undergoing liver resection in a single unit was undertaken. Posthepatectomy liver failure (PHLF) was defined according to the International Study Group of Liver Surgery (ISGLS) definition (assessed on day 5) and renal dysfunction according to RIFLE criteria. 90-day mortality was recorded. *Results*. Twenty-three patients died within 90 days of surgery (4.6%). The lowest mortality occurred in patients without evidence of PHLF or renal dysfunction (2.7%). The mortality rate in patients with isolated PHLF or renal dysfunction was 20% compared to 45% in patients with both. Diabetes ($P = 0.028$), renal dysfunction ($P = 0.030$), and PHLF on day 5 ($P = 0.011$) were independent predictors of 90-day mortality. *Discussion*. PHLF and postoperative renal dysfunction are independent predictors of 90-day mortality following liver resection but the predictive value for mortality is significantly higher when failure of both organ systems occurs simultaneously.

1. Introduction

Despite advances in both operative technique and perioperative care liver resection is associated with mortality rates of 0 to 22% (median 3.7%) and morbidity rates of 12.5% to 66% (median 36%) [1] including liver [2, 3] and renal dysfunction [4]. Liver dysfunction is a major contributor to both morbidity and mortality with an incidence between 1.2% and 32% in published series [5–12]. Renal dysfunction has also been shown to be associated with mortality following liver resection [13], with a reported incidence between 5 and 15% [4, 14]. Posthepatectomy renal failure may occur in conjunction with liver failure when maldistributive circulatory changes occur causing intravascular hypovolaemia [4, 15] but is also related to operative stress and blood loss [16, 17].

Postoperative liver dysfunction has been defined by the "50-50 criteria" as a prothrombin index of less than 50% (mean normal prothrombin time (PT) divided by patient's observed PT) and a serum bilirubin of >50 μmol/L on the fifth postoperative day, which has been shown to predict liver failure and death after hepatectomy [2]. More recently posthepatectomy liver failure (PHLF) has been defined by the International Study Group of Liver Surgery (ISGLS) as a postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinaemia on or after postoperative day five [18]. The ability of this newer definition of PHLF, using lower measures of dysfunction, to predict mortality has not been thoroughly assessed.

The aim of this study was to assess the utility of the ISGLS definition of PHLF on postoperative day 5 as a predictor of mortality and to determine the interaction of liver and renal dysfunction in predicting 90-day mortality after liver resection.

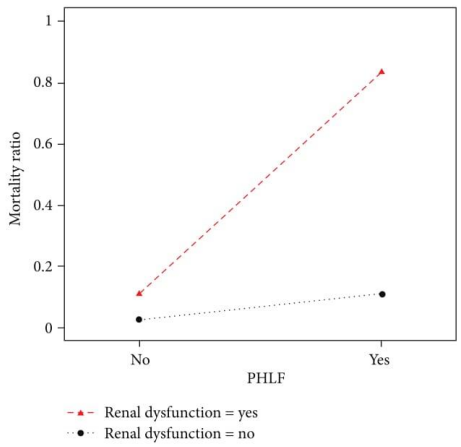

Figure 1: Mortality ratio of combined liver and renal dysfunction in 495 patients undergoing liver resection.

2. Materials and Methods

A retrospective analysis of a prospectively maintained database of all patients undergoing liver resection in this unit between July 2005 and September 2012 was undertaken. Five hundred and one patients were studied. Patient characteristics, laboratory data, and intraoperative details were retrieved. Liver resections were defined according to the Brisbane classification [19] and undertaken using standard techniques. Prior to resection the operating surgeon makes a visual assessment of the condition of the liver parenchyma and records this as normal or abnormal. Hepatic inflow occlusion was used in a minority of cases where there was excessive blood loss. The POSSUM scoring system was used to calculate the preoperative physiological risk score [20].

All patients were followed up for a minimum of 90 days and mortality was recorded along with details of the cause of death. The cause of death was determined from case-sheet review, radiological and laboratory data, and death certificates. Patients who died with jaundice and/or radiological evidence of ascites and/or encephalopathy in the absence of any other clear diagnosis were determined to have died of liver failure. Patients who died within 24 hours of surgery were excluded from further analysis as these deaths were most likely due to perioperative complications. Patients were also excluded if no postoperative blood tests were available.

Serum biochemistry tests and coagulation assays were performed on patients in the first 24 postoperative hours and the tests repeated according to clinical course. The peak measurement of bilirubin, prothrombin time (PT), and creatinine were recorded and used for analysis and patients with PHLF were identified as having an increased PT and serum bilirubin on postoperative day five according to the ISGLS definition [18]. In patients with preoperatively increased PT or serum bilirubin concentration PHLF was defined as an

Table 1: Preoperative and intraoperative characteristics of 501 patients undergoing hepatic resection.

$n = 501$	Median (range)	Count (%)
Age	65 (21–90)	
Gender		
Female		223 (45)
Male		278 (55)
Indication for surgery		
Benign		46 (9)
Primary		
Hepatocellular carcinoma		39 (8)
Cholangiocarcinoma		31 (6)
Others		28 (6)
Secondary		
Colorectal metastases		308 (61)
Other metastases		49 (10)
Liver directed chemotherapy		
Yes		176 (35)
No		325 (65)
Diabetes		
Yes		55 (11)
No		446 (89)
BMI	26 (16–54)	
ASA Grade		
1		51 (10)
2		323 (64)
3		124 (25)
4		2 (0.4)
Not recorded		1 (0.2)
Physiologic risk score	16 (12–32)	
Operative risk score	24 (14–35)	
Estimated P-POSSUM mortality (%)	7.7 (0.9–69.3)	
Confirmed fibrosis/cirrhosis		
Yes		22 (4)
No		479 (96)
Preoperative bilirubin (μmol/L)	9 (2–162)	
Preoperative haemoglobin (g/dL)	13.2 (8.6–17.0)	
Preoperative white cell count (/L)	6.9 (2.7–25.0)	
Preoperative albumin (g/L)	44 (24–53)	
Preoperative alkaline phosphatase (U/L)	95 (34–1190)	
Preoperative creatinine (μmol/L)	78 (40–430)	
Preoperative glomerular filtration rate (GFR)		
>90 mL/min		163 (33)

Table 1: Continued.

$n = 501$	Median (range)	Count (%)
<90 mL/min		326 (65)
Not measured		12 (2)
Preoperative neutrophil lymphocyte ratio (NLR)	2.5 (0.3–17.3)	
NLR > 5		
Yes		59 (12)
No		442 (88)
Open or laparoscopic approach		
Open		453 (90)
Laparoscopic		48 (10)
Radio frequency ablation (RFA) included		
Yes		23 (5)
No		478 (95)
Wedge resection included		
Yes		189 (38)
No		312 (62)
Operation		
Right hemihepatectomy		173 (35)
Extended right hemihepatectomy		34 (7)
Left hemihepatectomy		64 (13)
Extended left hemihepatectomy		17 (3)
Left lateral sectorectomy		48 (10)
Wedge resection only		133 (27)
Other		32 (6)
Bile duct reconstruction included		
Yes		46 (9)
No		455 (91)
Synchronous bowel procedure		
Yes		23 (5)
No		478 (95)
Operation number		
1st resection		465 (93)
2nd resection		31 (6)
3rd resection		5 (1)
Number of segments resected	4 (1–6)	
Number of procedures	1 (1–10)	
Surgeon's assessment of liver parenchyma		
Normal		323 (64)
Abnormal		171 (34)
Not recorded		7 (1)
Blood loss		
<500 mL		246 (49)
500–999 mL		175 (35)
≥1000 mL		76 (15)
Not recorded		4 (0.8)
Units transfused	0 (0–26)	

increasing serum bilirubin concentration and increasing PT on postoperative day 5 compared with the values of the previous day. It was not necessary to administer clotting factors to any surviving patients between postoperative days (POD) 1–5. Renal dysfunction was defined as an increase in serum creatinine of ≥1.5-fold from the preoperative baseline within the first five postoperative days, according to RIFLE criteria [21].

To determine potential associations between patient characteristics, operative factors, and organ dysfunction with 90-day mortality univariate logistic regression or chi-square test at the level of $P < 0.25$ [22] was performed, as appropriate. Significant variables in the univariate analysis were included in the multivariate logistic regression model and were considered to be significant if $P < 0.05$. Mortality ratios for organ failure were calculated as the proportion of deaths to proportion of survivors. All analyses were carried out using the statistical package R 2.1.14 [23].

3. Results

Five hundred one patients were studied. The indications for surgery and preoperative and operative details are shown in Table 1. Two patients who died within 24 hours of surgery were excluded from further analysis. One patient died of heart failure after a partially extended right hepatectomy and one died of biliary sepsis and multiorgan failure following an extended right hepatectomy for hilar cholangiocarcinoma. Details of twenty-one patients (4.6%) who died within 90 days of surgery are shown in Table 2. There was no significant difference in the median age of patients who died (71 years) and those who survived (65 years). The median interval to death after surgery was 31 days (7–89 days).

Of the 499 patients studied, blood tests were available in 495 patients (99.2%). Four patients did not have postoperative blood tests, all of whom had minor resections (fewer than three segments) and none of whom died within the study period and were excluded from analysis. A summary of liver and renal function tests in the whole cohort is shown in Table 3 along with the associated mortality.

PHLF occurred in 31 patients of whom two had pre-existing liver failure and 12 had extended resections. Seven patients in this group died within 90 days of surgery. Renal dysfunction also occurred in 31 patients, of whom 11 had extended resections. Seven patients in this group died within 90 days of surgery. In 55 patients with diabetes mellitus renal dysfunction occurred in seven patients (12.7%) compared to

Table 2: Details of 21 patients who died within 90 days of surgery. (Two patients who died within 24 hours of surgery were excluded.)

Cause of death	Count	Gender		Age	Right hepatectomy	Extended right	Extended left	Minor resection	Interval to death (days)
		Male	Female						
Liver failure	11	9	2	67 (58–76)	3	7	1	0	31 (11–83)
Malignancy	4	2	2	58 (43–76)	2	1	0	1	68.5 (14–86)
Sepsis	1	1	0	71	0	1	0	0	15
PE	1	1	0	71	1	0	0	0	7
Anastomotic leak	1	1	0	80	0	0	0	1	8
Peptic ulcer	1	0	1	81	1	0	0	0	22
Strangulated hernia	1	1	0	76	0	0	0	1	89
Peritonitis	1	1	0	76	0	0	0	1	70

Table 3: Postoperative liver and renal dysfunction in 495 patients undergoing hepatic resection (blood tests not performed in four patients).

Laboratory parameters at day 5 ($n = 495$)	Count (%)	90-day mortality (%)	Death due to liver failure
No PHLF or renal dysfunction	444 (89.7)	12 (2.7)	4
PHLF alone	20 (4.0)	2 (10)	2
Renal dysfunction alone	20 (4.0)	2 (10)	2
Renal dysfunction plus PHLF	11 (2.2)	5 (45.5)	3

24 of 440 patients without diabetes (5.5%) ($P = 0.067$). No patient with diabetes and normal preoperative renal function ($n = 12$) developed postoperative renal dysfunction compared to seven of 43 diabetic patients with impaired preoperative renal function ($P = 0.326$).

The lowest mortality (2.7%) occurred in the 444 patients without laboratory evidence of PHLF or renal dysfunction at day five, of whom 12 died, compared to 9 of 51 (17.6%) patients with either or both of these diagnoses. In the first group four of the twelve deaths were due to liver failure compared to seven of the nine deaths in the group with evidence of organ dysfunction at POD 5.

The mortality rate in patients who fulfilled the criteria for PHLF on POD 5 but did not have renal dysfunction was identical (2 of 10 patients) to that of patients with renal dysfunction without PHLF (2 of 10 patients). All four of these patients died of liver failure. Mortality was greatest in the group of eleven patients with both PHLF and renal dysfunction of whom five died. Three of these five patients died of liver failure, one from anastomotic leak, and one from a bleeding peptic ulcer.

Multivariate analysis of potential risk factors for mortality including postoperative organ dysfunction (Table 4) revealed that the only preoperative factor independently associated with 90-day mortality was the presence of diabetes ($P = 0.028$), which more than trebled the risk of 90-day mortality.

Both PHLF on POD 5 and postoperative renal dysfunction were independently associated with 90-day mortality. PHLF at POD 5 increased the risk of 90-day mortality by a factor of 4.5 ($P = 0.011$) and renal dysfunction increased the risk by a factor of 3.6 ($P = 0.030$).

The positive predictive value (PPV) for mortality in patients who fulfilled the criteria for PHLF (including those with and without renal dysfunction) was 22.6%. However within this group the PPV was much lower (10%) if the criteria for PLF were fulfilled with normal renal function (Table 5). The PPV for mortality of fulfilling the criteria for PHLF with concurrent renal dysfunction was 45%.

The effect of developing renal dysfunction in the context of PHLF is demonstrated by the greater than fourfold increase in mortality ratio (Figure 1).

4. Discussion

The principle findings of this study are that PHLF on POD 5 as defined by the ISGLS and postoperative renal dysfunction are independent predictors of 90-day mortality following liver resection. The predictive value for mortality is significantly higher when failure of both organs occurs, with a PPV of 45% and NPV of 97%. Preoperative diabetes mellitus is also an independent predictor of 90-day mortality.

The 90-day mortality (4.6%) in this series is similar to results of other units [1]. An important observation is that half the postoperative deaths in the series occurred between 31 and 90 days after surgery, stressing the importance of reporting 90-day rather than 30-day mortality. Of the 21 postoperative deaths 11 were found to be due to liver failure.

The study confirms the ability of PHLF to predict 90-day mortality. Interestingly however the majority of patients who developed PHLF at POD 5 (24 of 31) recovered whilst six of the eleven patients who died of liver failure did not fulfil the ISGLS definition of PHLF at POD 5. Only one patient in this series fulfilled the "50-50 criteria" of postoperative liver dysfunction, who subsequently recovered. Therefore the "50-50" criteria had no value as a predictor of liver failure or mortality in this series with a PPV of zero. In comparison the ISGLS definition of PHLF has lower thresholds for abnormal bilirubin and PT and is a more clinically useful tool for

Table 4: Univariate and multivariate analysis of preoperative and operative factors as well as postoperative blood tests associated with 90-day mortality following liver resection in 495 patients.

$n = 495$	Univariate		Multivariate	
Factor (preoperative and operative factors and postoperative blood tests)	Coef (95% CI)	P value	Coef (95% CI)	P value
Age	1.05 (1.01–1.10)	0.029*		0.194
Gender	2.36 (0.91–6.08)	0.077*		0.196
Pathology		0.274		
Liver directed chemotherapy		0.356		
Diabetic	3.09 (1.16–8.20)	0.024*	3.41 (1.14–10.23)	0.028**
BMI		0.444		
ASA grade				
1 versus 2	3.02 (0.70–13.11)	0.139*		0.678
2 versus 3		0.724		
Physiologic score	1.12 (1.03–1.22)	0.010*		0.544
Operative score		0.303		
P-POSSUM mortality	1.04 (1.01–1.07)	0.010*		0.479
Fibrosis/cirrhosis		0.986		
Preoperative bilirubin	1.01 (1.00–1.03)	0.081*		0.652
Preoperative haemoglobin	0.71 (0.55–0.93)	0.012*		0.195
Preoperative white cell count		0.388		
Preoperative albumin	0.90 (0.84–0.96)	0.002*		0.168
Preoperative alkaline phosphatase		0.884		
Preoperative creatinine	1.01 (1.00–1.02)	0.098*		0.764
Preoperative neutrophil lymphocyte ratio	1.13 (0.98–1.31)	0.086*		0.366
Preoperative neutrophil lymphocyte ratio >5	2.18 (0.78–6.11)	0.138*		0.345
Open or laparoscopic resection		0.987		
Radiofrequency ablation (RFA) included		0.991		
Wedge resection included		0.588		
Bile duct reconstruction included	2.96 (1.05–8.39)	0.041*		0.383
Synchronous bowel procedure		0.346		
Operation number		0.549		
Number of segments resected	1.59 (1.18–2.14)	0.003*		0.075
Number of procedures		0.786		
Surgeons assessment of liver parenchyma	2.14 (0.92–4.96)	0.076*		0.494
Blood loss (mL)				
<500 versus >500	2.67 (1.27–5.61)	0.009*		0.716
>500 versus >1000		0.652		
Units of red cells transfused	1.13 (1.02–1.26)	0.023*		0.224
PHLF at POD 5	1.02 (1.01–1.03)	<0.001*	4.51 (1.42–14.40)	0.011**
Renal dysfunction (creatinine rise >1.5x)	1.02 (1.01–1.03)	<0.001*	3.63 (1.13–11.66)	0.030**

*Significant at the level of 0.25 for univariate analysis and included in multivariate analysis.
**Significant at the level of 0.05 for multivariate analysis.

the prediction of 90-day mortality with a PPV of 23% and NPV 97%. This is similar to the findings of the only other study to address this issue, which revealed that the PPV and NPV of PHLF were 32% and 98%, respectively [24]. Simple blood tests therefore have a low positive predictive value for mortality due to liver failure.

Renal dysfunction occurred in 6.3% of patients which is similar to other published series [4, 14]. Renal dysfunction

Table 5: Predictive values of PHLF and renal dysfunction within the first five postoperative days in 495 patients undergoing liver resection.

	Positive predictive value (PPV)	Negative predictive value (NPV)
No PHLF or renal dysfunction	0.027	0.824
PHLF alone	0.1	0.970
Renal dysfunction alone	0.1	0.970
PHLF and renal dysfunction	0.455	0.967

following liver resection may occur as a consequence of liver failure and hepatorenal syndrome but may also result from hypovolaemia or damage from inflammatory mediators during surgery [4]. This occurs more commonly in elderly patients with atherosclerosis or hypertension [15]. These mechanisms of renal dysfunction may occur simultaneously. The use of low central venous pressure (CVP) during resection may also increase the risk of postoperative renal dysfunction [25, 26]. The results of this study demonstrate that isolated renal dysfunction is a significant risk factor for mortality independent of the development of PHLF. Interestingly the two patients with isolated renal dysfunction in the first five postoperative days subsequently died of liver failure. This may be attributed to renal dysfunction delaying the onset of hepatic regeneration [27]. The most marked mortality effect of renal dysfunction was seen in conjunction with PHLF, where the mortality rate increased by a factor of four. Therefore, although the ISGLS definition of PHLF is able to predict mortality due to liver failure the development of renal dysfunction in this context is the single most important predictive factor.

The finding of the significance of diabetes as a risk factor for postoperative mortality confirms earlier findings [28]. Insulin is important for hepatic function and regeneration [29] and diabetes is also a risk factor for the development of nonalcoholic fatty liver disease and cirrhosis [30] which may lead to higher rates of PHLF [31]. Diabetic nephropathy is also a major cause of renal dysfunction [32].

In conclusion we have demonstrated that PHLF as defined by the ISGLS on postoperative day five and postoperative renal dysfunction are able to predict 90-day mortality following liver resection, although most patients fulfilling these criteria of organ dysfunction will recover. In addition many patients will succumb to liver failure without fulfilling the PHLF criteria in the early postoperative period. The combination of these two markers of organ dysfunction is the best early predictor of mortality following liver resection and we suggest that PHLF and postoperative renal dysfunction should be used in conjunction when predicting mortality after liver resection.

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ORIGINAL ARTICLE

Extended pathology reporting of resection specimens of colorectal liver metastases: the significance of a tumour pseudocapsule

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Abstract

Introduction: The aim of this study was to analyse the influence of factors reported in the minimum histopathology dataset for colorectal liver metastases (CRLM) and other pre-operative factors compared with additional data relating to the presence of tumour pseudocapsules and necrosis on recurrence 1 year after a resection.

Methods: For a period of 14 months, extended histological reporting of CRLM specimens was performed, including the presence of pseudocapsules and necrosis in each tumour. The details of recurrence were obtained from surveillance imaging.

Results: In 66 patients there were 27 recurrences within 1 year. The rates were lower for patients with tumour pseudocapsules (8/27) than for patients without (19/36) (P = 0.030). Pseudocapsules were associated with a younger age (P = 0.005), nodal stage of the primary colorectal tumour (P = 0.025) and metachronous tumours (P = 0.004). In patients with synchronous disease and pseudocapsules, the recurrence rate was 2/12 compared with 13/23 patients without pseudocapsules (P = 0.026).

Discussion: These findings demonstrate that histological examination of resection specimens can provide significant additional prognostic information for patients after resection of CRLM, compared with clinical and radiological data. The present finding that the absence of a pseudocapsule in patients with synchronous CRLM is associated with a dramatically worse outcome may help direct patient-specific adjuvant treatment and care.

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Introduction

Although resection of colorectal liver metastases (CRLM) offers overall 5-year survival rates ranging from 32–65%,[1,2] there is a spectrum of outcomes after surgery with some individuals remaining disease free and potentially being cured, whereas others will recur early with a poor outcome.[3,4] A number of risk scoring systems exist to stratify patients according to likely 5-year survival. These systems predominantly use factors measurable pre-operatively which have been shown to be markers of prognosis, such as carcinoembryonic antigen (CEA) estimation,[5] tumour number,[5–15] tumour size,[5,12–15] resection margin clearance,[5,8–10,12,16–20] the presence of satellite lesions[18] and the ratio of neutrophils to lymphocytes amongst white cells in a full blood count measured pre-operatively.[21] Liver specimens are routinely sent for pathological analysis after resection and the UK Royal College of Pathologists (RCPath) minimum dataset for liver specimens with colorectal metastases includes details of tumour number, size, location, resection margin clearance, capsular invasion, degree of differentiation, the presence of tumour necrosis, vascular and lymphatic invasion, the presence of satellite lesions, invasion of adherent tissue and lymph node status if sampled.[22] With regards to prognostic factors, the most important additional information the pathology report reveals which is not available pre-operatively is the resection margin status. However, of the 15 risk scoring systems available, only 3 have shown the presence of an involved resection margin to be a significant prognostic factor.[23] Therefore histological examination

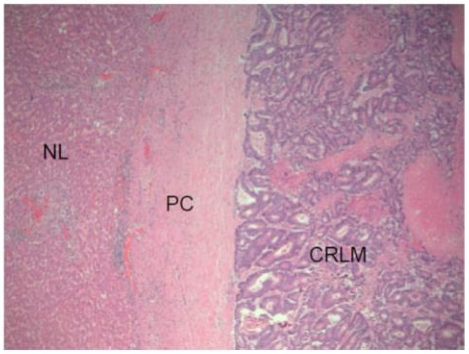

Figure 1 Pathological examination showing a pseudocapsule (PC), non-neoplastic liver (NL) and a colorectal liver metastasis (CRLM). Original magnification x50 using haematoxylin and eosin stain

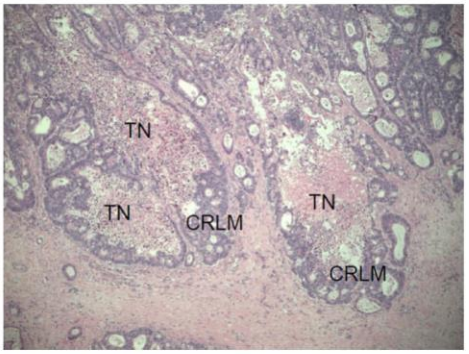

Figure 2 Pathological examination showing tumour necrosis (TN) in colorectal liver metastases (CRLM). Original magnification x50 using haematoxylin and eosin stain

of CRLM specimens may add relatively little additional prognostic information compared with clinical, radiological and laboratory data in the currently used scoring systems.

Extended examination of resection specimens may reveal other features whose prognostic significance has not been rigorously assessed, including details of a fibrous pseudocapsule around the tumour and the degree of tumour necrosis. The presence of a pseudocapsule has been associated with a better overall survival after resection of CRLM.[24–26] Tumour necrosis can result from chemotherapy use[27] and is also seen in tumours with high rates of cellular turnover in rapidly expanding tumours.[28] Therefore tumour necrosis may be associated with more aggressive tumours and a worse prognosis.

The aim of this study was to analyse the relative significance of factors reported in the minimum histopathology dataset and other pre-operative factors compared with additional data relating to the presence of tumour pseudocapsules and necrosis on tumour recurrence 1 year after resection of CRLM.

Methods

Between March 2010 and May 2011, the Histopathology Department at Derriford Hospital performed extended reporting of CRLM specimens as an experimental protocol. Histology reports documented the presence or absence of a pseudocapsule, as well as how much of each tumour diameter was encompassed (zero, <50% or >50%). The presence and degree of necrosis observed in each tumour (nil, <33%, 33–66% and complete necrosis) was also recorded. Up to a maximum of the three largest tumours in each patient were assessed and relevant features recorded. The pseudocapsule was identified as a paucicellular collagenous band present between the tumour cells and the adjacent hepatocytes, which measured at least 0.1 mm in thickness (Fig. 1). Tumour necrosis was characterized as discrete foci of cellular debris indicative of coagulative cell death (Fig. 2). A proforma was designed and agreed within the Histopathology department to standardize reporting of resection specimens. In cases of heterogeneity between tumours, the amount of pseudocapsule in up to the three largest tumours was measured and an average figure calculated according to a simple formula (>50% = 2, <50% = 1, no pseudocapsule = 0) and used in analyses. The amount of necrosis was determined for the largest lesion only.

All patients underwent tumour staging with a computed tomography scan prior to surgery. In addition, 46 patients had a pre-operative magnetic resonance imaging (MRI) scan and 50 patients a pre-operative positron emission tomography (PET) scan, at the discretion of the referring clinician.

A prospective database is maintained of all patients undergoing resection for CRLM and a review of these patients was performed when all had been followed up for a minimum of 1 year. The database holds information on primary histology, timing of detection of metastatic disease (synchronous tumours were defined as those discovered pre-operatively or within 2 months of primary surgery), the neutrophil to lymphocyte ratio, the use of chemotherapy as well as the histological features of the resected CRLM. Details of tumour recurrence were identified from surveillance imaging which is performed according to published guidelines.[22] CEA estimation was not used routinely in post-operative surveillance. One patient did not have surveillance imaging in the first post-operative year and was excluded from recurrence analysis. One-year recurrence was chosen as the primary end point because a high proportion of CRLM recur within this timeframe and early recurrence is associated with a worse overall survival.[3,4]

Potential associations between 1-year tumour recurrence and clinical and histological characteristics were tested initially using

Table 1 Pre-operative details of 66 patients undergoing extended histological reporting of resection of hepatic colorectal metastases

n = 66		Median (range)	Count (%)
Age		65 (33–84)	
Gender	Male		40 (60.6)
	Female		26 (39.4)
Primary T stage	0		2 (3.0)
	1		3 (4.5)
	2		7 (10.6)
	3		29 (43.9)
	4		23 (34.8)
	Unavailable		2 (3.0)
Primary N stage	0		34 (51.5)
	1		18 (27.2)
	2		11 (16.7)
	Unavailable		3 (4.5)
Timing	Synchronous		38 (57.6)
	Metachronous		28 (42.4)
Liver-directed chemotherapy	Synchronous		35 (92.1)
	Metachronous		11 (39.2)
Neutrophil lymphocyte ratio	Less than 5		57 (86.4)
	More than 5		9 (13.6)

univariate logistic regression or the chi-square test at the level of $P < 0.25$,[29] as appropriate. The association between clinical and histological characteristics and the presence of a tumour pseudocapsule in individual tumours was tested in a similar fashion. Significant variables in the univariate analysis were included in the multivariate logistic regression model and were considered to be significant if $P < 0.05$. All analyses were carried out using the statistical package R 2.1.14.[30]

Results

Sixty-six patients were identified who underwent surgery for CRLM of whom 65 were available for recurrence analysis. Additional staging MRI scans were performed in 28 of 38 patients with synchronous tumours and 18 of 28 with metachronous tumours ($P = 0.431$). Additional staging PET scans were performed in 28 of 38 patients with synchronous tumours and 22 of 28 with metachronous tumours ($P = 0.774$). The median number of surveillance scans performed was one (1–4) in patients who recurred and two (1–5) in patients who had not recurred at 1 year.

In addition to surgery, four patients had intra-operative radiofrequency ablation (RFA). Six patients died of recurrent cancer in the first year of follow-up. Twenty-eight patients (43.1%) developed recurrent cancer within the first year of follow-up. Eight of these recurred in the liver only, 12 had extrahepatic recurrence only and 8 had both hepatic and extrahepatic recurrence. Patient characteristics are displayed in Table 1.

From the total patient group, 132 lesions were examined histologically in the extended dataset. In two patients, three tumours had responded completely to chemotherapy and were only identifiable microscopically as areas of complete necrosis. In these tumours, the presence of a pseudocapsule could not be assessed. Histological details of the resected specimens including the RCPath dataset and the presence of a pseudocapsule and degree of tumour necrosis for the 65 patients included in the recurrence analysis are shown in Table 2. Heterogeneity in the presence of tumour pseudocapsules in multiple metastases was observed in 6 of 27 patients, where pseudocapsules were absent in some tumours, and in 5 of 27 patients where a differing amount of pseudocapsule was noted between tumours.

Analysis of factors associated with 1-year recurrence in 65 patients

Univariate analysis of pre-operative and histological factors and 1-year recurrence revealed potential associations with age, number of metastases, a resection margin of less than 1 mm and the presence or absence of a pseudocapsule ($P < 0.250$) (Table 3). Multivariate analysis revealed that only the absence of a pseudocapsule and a resection margin of less than 1 mm were significantly associated with early tumour recurrence (Table 3). One-year recurrence rates were lower for patients with tumour pseudocapsules (8/27) than for patients with no pseudocapsule (19/36) ($P = 0.030$). There was no significant difference in tumour recurrence rates according to the amount (< or >50%) of pseudocapsule present ($P = 0.750$) (Fig. 3). The recurrence rate in patients with a resection margin of <1 mm was 13/22 compared with 15/43 in those with a margin of >1 mm ($P = 0.045$).

Table 2 Histopathological features and 1-year recurrence of 65 patients undergoing extended histological reporting of resection of hepatic colorectal metastases with 1-year follow-up

n = 65		1-year recurrence			
		No (*n* = 37)		Yes (*n* = 28)	
		Median (range)	Count	Median (range)	Count
Number of lesions identified		2 (1–10)		3 (1–10)	
Max diameter at histology (mm)		27 (3–119)		43 (7–120)	
Satellite lesions	Yes (0)		0		0
	No (65)		37		28
Margin less than 10 mm	Yes (45)		24		21
	No (20)		13		7
Margin less than 1 mm	Yes (22)		9		13
	No (43)		28		15
Liver capsule smooth and intact	Yes (55)		33		22
	No (10)		4		6
Invasion of adherent tissue	Yes (1)		0		1
	No (64)		37		27
Differentiation	No tumour (3)		2		1
	Well/moderate (62)		35		27
Vascular invasion	Yes (9)		3		6
	No (56)		34		22
Histological evidence of response to chemotherapy	No response (4)		2		2
	Response (19)		13		6
	Uncertain (7)		4		3
	Not recorded (35)		18		17
Average amount of pseudocapsule	Nil (36)		17		19
	<50% (17)		12		5
	>50% (10)		7		3
	N/A (2)		1		1
Amount of necrosis of the largest tumour	Nil (4)		3		1
	<33% (29)		16		13
	33–66% (21)		13		8
	>66% (11)		5		6

In two patients (three tumours) a complete response to chemotherapy was noted and therefore a pseudocapsule could not be identified (NA).

Analysis of factors associated with the presence of a pseudocapsule in 132 tumours

Uni- and multivariate analysis was undertaken and revealed that increasing age, nodal status of the primary colorectal cancer and metachronous liver metastases were associated with the presence of a tumour pseudocapsule (Table 4). The size of individual tumours was not associated with the presence of a pseudocapsule. For each year of age the incidence of a pseudocapsule falls by 0.073 (Fig. 4). Similarly as the N stage increases by 1, the incidence of a pseudocapsule falls by 0.566 (Fig. 5). Pseudocapsules occurred more commonly in tumours with a metachronous presentation (25/51) compared with a synchronous presentation (20/81) ($P = 0.004$). Resection margin positivity was noted in 11 of 52 tumours with a pseudocapsule and 8 of 77 tumours without a pseudocapsule ($P = 0.105$).

The presence of a pseudocapsule had no significant association with 1-year recurrence in patients with metachronous CRLM. However, in individuals with synchronous lesions the presence of a pseudocapsule was associated with a lower 1-year recurrence rate (2/12 versus 13/23) ($P = 0.026$) (Table 5).

Discussion

The principal finding of this study is that a fibrous pseudocapsule is a common histological feature in patients undergoing resection

Table 3 Univariate and multivariate analysis of pre-operative and histological factors affecting 1-year recurrence after resection of hepatic colorectal metastases in 65 patients

Factor (n = 65)	Univariate P-value	Multivariate P-value	Incidence ratio (95% CI)
Age	0.025[a]	0.876	
Gender	0.506		
Max diameter of tumour at histology	0.323		
Number of lesions	0.240[a]	0.831	
Capsule smooth and intact	0.408		
Margin less than 1 mm	0.109[a]	0.045[b]	2.89 (1.61– 5.18)
Margin less than 10 mm	0.545		
Histological response to chemotherapy	0.674		
T stage of primary tumour	0.571		
N stage of primary tumour	0.381		
Synchronous versus metachronous	0.824		
Liver directed chemotherapy (yes/no)	0.710		
Neutrophil lymphocyte ratio (>5)	0.320		
Pseudocapsule present	0.114[a]	0.030[b]	0.30 (0.174–0.524)
Necrosis of largest lesion	0.886		

[a]Significant at the level of 0.25 for univariate analysis and included in multivariate analysis.
[b]Significant at the level of 0.05 for multivariate analysis.

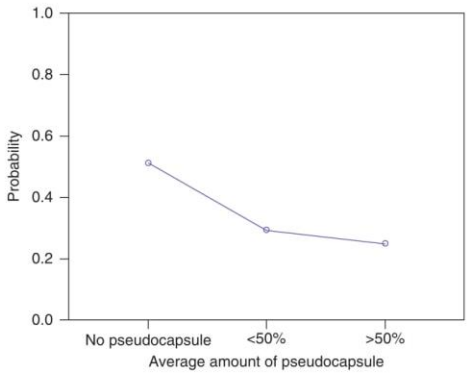

Figure 3 Probability of 1 year recurrence according to the amount of pseudocapsule present for 65 patients undergoing extended histological reporting of resection of hepatic colorectal metastases. No significant difference between <50% and >50% (P = 0.75)

of CRLM and is associated with a lower 1-year tumour recurrence rate. This study extends earlier reports by showing that the benefit of a pseudocapsule occurs predominantly in patients with synchronous hepatic metastases. In these patients, only one-third develop a pseudocapsule but have a dramatically reduced incidence of 1-year tumour recurrence (2/12) compared with patients without a pseudocapsule (13/23). The study also confirms that the presence of an involved resection margin is an independent predictor of early tumour recurrence. These two findings demonstrate that histological examination of resection specimens can provide significant additional prognostic information for patients after resection of CRLM, compared with clinical and radiological data available pre-operatively.

The strength of the study lies in its prospective and unselected design, including all patients over a defined period with standardization of reporting within predetermined guidelines. Specimens were reported by pathologists with a subspecialty interest in gastrointestinal disease who collectively approved the experimental protocol. The value of these findings to clinical practice is significant as the identification of a tumour pseudocapsule is readily performed on standard histology specimens without the need for special stains. A potential weakness of the study is that estimation of the extent of the pseudocapsule is subjective and semi-quantitative; however, the present data show that the extent of the pseudocapsule is less important than its simple presence.

Although three previously published studies have shown that the presence of a pseudocapsule is associated with improved long-term survival after resection of CRLM[24–26] it is not commonly reported in this setting. Our series is the first to report lower recurrence rates in the presence of a tumour pseudocapsule in a Western population and adds further evidence of the benefit of adding this finding to the core data set in histology reporting of CRLM. Further follow-up will determine if lower early recurrence rates in this group are associated with an improved survival.

Table 4 Univariate and multivariate analysis of factors associated with the presence of a tumour pseudocapsule (n = 132) in 66 patients undergoing resection of hepatic colorectal metastases

Factor (n = 132)	Univariate P-value	Multivariate P-value	Incidence ratio (95% CI)
Age (per year)	0.011[a]	0.005[b]	0.937 (0.90–0.98)
Gender	0.090[a]	0.142	
T stage of primary tumour	0.290		
N stage of primary tumour	<0.001[a]	0.025[b]	0.434 (0.24–0.77)
Metachronous versus synchronous	0.004[a]	0.004[b]	2.622 (1.13–6.09)
Neutrophil lymphocyte ratio	0.348		
Tumour size	0.167[a]	0.405	
Resection margin < 1 mm	0.150[a]	0.105	

[a]Significant at the level of 0.25 for univariate analysis and included in multivariate analysis.
[b]Significant at the level of 0.05 for multivariate analysis.

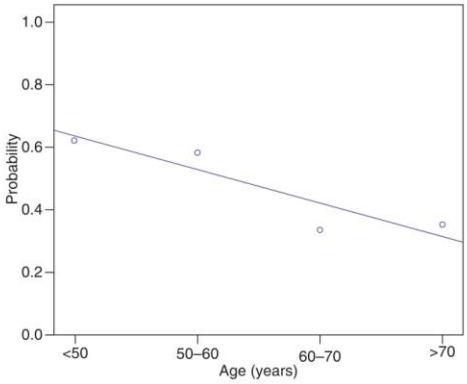

Figure 4 Probability of pseudocapsule presence according to age for 132 tumours in patients undergoing resection of hepatic colorectal metastases

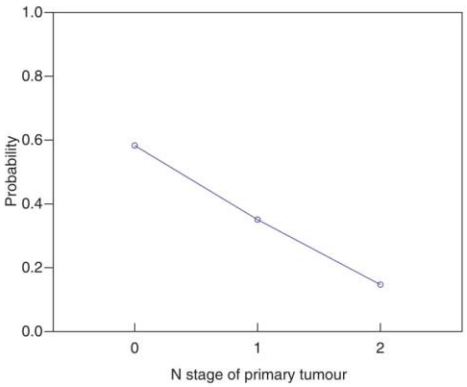

Figure 5 Probability of a pseudocapsule according to N stage of primary colorectal tumour for 132 tumours in patients undergoing resection of hepatic colorectal metastases

Table 5 Relationship between pseudocapsule and 1-year recurrence in synchronous and metachronous lesions in patients undergoing resection of hepatic colorectal metastases

n = 65				1-year recurrence		
				No	Yes	P-value
Timing	Synchronous (37)	Pseudocapsule	Absent (23)	10	13	0.026[a]
			Present (12)	10	2	
			N/A (2)	1	1	
	Metachronous (28)	Pseudocapsule	Absent (13)	7	6	0.521
			Present (15)	9	6	

[a]Significant at the level of 0.05 on Fisher's exact test.

It is not known what stimulates the formation of a fibrous pseudocapsule and what role it plays in preventing early recurrence. The capsule develops at the interface between tumour tissue and normal liver tissue and the proliferating stromal cells in the capsule have been shown to be myofibroblasts.[26] It has been suggested that CRLM activate hepatic stellate cells to form myofibroblasts and that this is a host defence response, similar to an inflammatory response, creating a mechanical and chemical

barrier around the tumour preventing further vascular and intrabiliary invasion.[26] The present finding that the absence of a tumour pseudocapsule is associated with a more aggressive primary tumour with nodal metastases supports this hypothesis, although we did not find any association with the neutrophil to lymphocyte ratio among circulating leucocytes, which has also been shown to be a marker of an inflammatory response to the tumour.[21] It is also possible that older patients are less able to generate an inflammatory response to the tumour, accounting for the finding of a smaller proportion with tumour pseudocapsules in this age group.

The present finding that the absence of a pseudocapsule in patients with synchronous CRLM is associated with a higher tumour recurrence may help direct patient-specific adjuvant treatment and care. For example, these patients may benefit from an increased frequency of post-operative imaging surveillance. Although post-operative chemotherapy after resection of CRLM has been shown to be of a limited value,[31] future trials of this modality may be developed to target treatment to high-risk groups, such as patients with synchronous tumours with no pseudocapsules.

Further research needs to be undertaken to confirm the potential association of a lower tumour recurrence rate in patients with tumour pseudocapsule in larger series, in addition to correlating this finding with improved survival. Further data may allow the development of a risk scoring system incorporating this finding.

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Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Socioeconomic status influences the likelihood but not the outcome of liver resection for colorectal liver metastasis

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Abstract

Background: The aim of this study was to compare the socioeconomic profile of patients undergoing liver resection for colorectal liver metastasis (CLM) in a regional hepatopancreatobiliary unit with that of the local population. A further aim was to determine if degree of deprivation is associated with tumour recurrence after resection.

Methods: A retrospective analysis of patients undergoing liver resection for CLM was performed. Geodemographic segmentation was used to divide the population into five categories of socioeconomic status (SES).

Results: During a 7-year period, 303 patients underwent resection for CLM. The proportion of these patients in the two least deprived categories of SES was greater than that of the local population (50.2% versus 40.2%) and the proportion in the two most deprived categories was lower (18.3% versus 30.1%) ($P < 0.001$). There was no difference in recurrence rate ($P = 0.867$) or disease-free survival among categories of SES ($P = 0.913$). Multivariate analysis demonstrated no association between SES and tumour recurrence ($P = 0.700$).

Conclusions: Liver resection for CLM is performed more commonly among the least socioeconomically deprived population than among the most deprived. However, degree of deprivation was not associated with tumour recurrence after resection.

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Introduction

The incidence of primary colorectal cancer is associated with low socioeconomic status (SES) in the UK, where the age-standardized incidence is 11% higher in men living in the most deprived areas of England compared with those living in the least deprived,[1] although no difference has been demonstrated in women. Similar associations have been found in the USA, where individuals with higher levels of deprivation have been found to have a greater risk for the development of colorectal cancer even when other risk factors are controlled for.[2] Population studies have also shown that low SES is associated with a worse outcome amongst patients with colorectal cancer.[3–5] Approximately a quarter of patients with colorectal cancer will develop colorectal liver metastases (CLM) at the time of presentation[6] and a further 25–30% will develop CLM within 2–3 years of diagnosis.[7] Little is known of the impact of SES on the risk for CLM and on outcomes of liver resection: a single UK study demonstrated no association between social class and longterm outcome following resection.[8] However, this study did not account for potential bias caused by patient selection for liver surgery. Patients with primary colorectal cancer often present symptomatically and are at risk of colonic obstruction, and population studies have shown that 60–80% of patients with primary colorectal cancer will be offered surgery.[9] However, the proportion of patients with CLM who are offered surgery is far lower, at 10–20%.[10,11] Patients who develop CLM must overcome a number of potential obstacles before undergoing liver surgery. They must survive surgery for primary colorectal

cancer; they require longterm surveillance imaging to detect metachronous lesions; they must be referred to a hepatobiliary unit; they must be medically fit for surgery, and their metastases must be technically resectable. Socioeconomic factors may influence a patient's ability to overcome these obstacles following surgery for primary colorectal cancer, which may potentially skew the population of patients submitted to surgery for CLM in comparison with that of the population suffering primary colorectal cancer. A crude comparison of outcomes according to SES may therefore be less valid for CLM as patients may be more stringently selected than those undergoing surgery for primary colorectal cancer.

The primary aim of this study was to compare levels of socioeconomic deprivation in patients undergoing liver resection for CLM in a regional hepatopancreatobiliary (HPB) unit with those of the local population. A secondary aim was to determine if SES is associated with disease-free and overall survival.

Materials and methods

A retrospective analysis of a prospectively maintained database of all patients submitted to liver resection for CLM between July 2005 and March 2012 was undertaken. Patient details, laboratory data and operative details were retrieved. Synchronous metastases were defined as those diagnosed prior to or within 2 months of primary surgery. All patients underwent tumour staging with computed tomography (CT) prior to liver surgery. Preoperative magnetic resonance imaging (MRI) and positron emission tomography (PET) scans were performed at the discretion of the referring clinician. The physiological score was calculated using the POSSUM (*p*hysiological and *o*perative *s*everity *s*core for the en*u*meration of *m*ortality and morbidity) scoring system.[12] Postoperative surveillance CT scans were performed at 6-monthly intervals for 3 years after liver resection and annually for another 2 years. All patients included in disease-free survival analyses underwent a minimum of one surveillance CT scan and the date of tumour recurrence was recorded.

Socioeconomic status was calculated using ACORN®,[13] a commercially available geodemographic segmentation tool. This tool divides UK households into five categories in order of increasing deprivation, characterized as representing: wealthy achievers; the urban prosperous; the comfortably off; those of moderate means, and the hard-pressed. The smallest unit of population for which information is available is based on postcode. Full postcodes allow an accurate geographical breakdown because the median size of a residential postcode in the UK is 13 households or 31 residents.[13] The deprivation category is based on data collected from multiple sources including property value, type, occupancy and usage. Further information relating to residents is obtained and includes data on date of birth, ethnicity and receipt of social benefits, along with data on spending habits and lifestyle. Population density data are obtained from the National Census.

Patient survival curves were constructed using the Kaplan–Meier method and differences in survival were assessed using the log-rank method. Patients were excluded from survival analyses if they underwent planned non-curative resections or did not receive surveillance imaging. Comparisons between groups according to SES were performed using the chi-squared test or Mann–Whitney *U*-test, as appropriate. Potential associations between pre- and intraoperative factors, as well as histological outcome and tumour recurrence, were tested using univariate logistic regression or the chi-squared test, as appropriate. Variables in the univariate analysis for which differences achieved a *P*-value of <0.25 were included in the multivariate regression model.[14] Differences were considered to be significant at $P < 0.05$. Univariate and multivariate analyses were carried out using R Version 2.1.14.[15]

Patient consent was not required for this study following confirmation from the South West Health Research Authority that under the harmonized Guidance Approval for Research Ethics Committees (RECs), REC review is not required because patient data were collected in the course of normal hospital care and were anonymized for research purposes.

Results

Data relating to 303 liver resections performed for CLM over a period of 7 years were analysed. Clinicopathological characteristics and operative details of the group are displayed in Table 1. The proportions of residents of Devon and Cornwall in the first and second (least deprived) (40.2%) and fourth and fifth (most deprived) (30.1%) SES categories differed from those of the UK (37.4% and 35.1%, respectively) ($P < 0.001$) (Table 2). Socioeconomic data were unavailable for eight patients undergoing liver resection, leaving 295 for analysis. Of these 295 patients submitted to liver resection for CLM, the proportions of patients from the first and second (least deprived) categories (50.2%) and fourth and fifth (most deprived) categories (18.3%) of SES differed from the proportions in the local population (40.2% and 30.1%, respectively) ($P < 0.001$).

The clinicopathological and operative characteristics of the 148 least deprived (categories 1 and 2) and 54 most deprived (categories 4 and 5) patients are displayed in Table 3. The use of PET scans was greater in the least deprived than in the most deprived group (75.0% versus 46.3%) and the proportion of patients with American Society of Anesthesiologists (ASA) class 1 status was higher in the least deprived (10.8%) compared with the most deprived (1.9%) group.

Data for 18 patients were excluded from the disease-free survival analysis because their resections were non-curative or they did not complete a staged resection. Data for a further 11 patients were excluded because these patients died without undergoing surveillance imaging. This left a total of 266 patients for analysis. The median length of follow-up was 1.07 years (range: 0.14–6.59 years) in the least deprived categories and 1.14 years (range:

Table 1 Preoperative and operative characteristics of 303 patients undergoing liver resection for colorectal liver metastases

		Value
Age, years, median (range)		67 (33–90)
Gender, *n* (%)	Female	113 (37.3%)
	Male	190 (62.7%)
T stage of primary, *n* (%)	0	3 (< 1%)
	1	7 (2.3%)
	2	19 (6.3%)
	3	174 (57.4%)
	4	91 (30.0%)
	Unavailable	9 (3.0%)
N stage of primary, *n* (%)	0	133 (43.9%)
	1	101 (33.3%)
	2	64 (21.1%)
	Unavailable	5 (1.7%)
Site of primary, *n* (%)	Colonic	152 (50.2%)
	Rectal	151 (49.8%)
Timing, *n* (%)	Synchronous	144 (47.5%)
	Metachronous	159 (52.5%)
Preoperative MRI, *n* (%)	Yes	166 (54.8%)
	No	137 (45.2%)
Preoperative PET, *n* (%)	Yes	208 (68.6%)
	No	95 (31.4%)
Preoperative liver-directed chemotherapy, *n* (%)	Yes	151 (49.8%)
	No	152 (50.2%)
Preoperative diabetes, *n* (%)	Yes	28 (9.2%)
	No	275 (90.8%)
BMI, kg/m^2, median (range)		27 (16–54)
ASA class, *n* (%)	1	24 (7.9%)
	2	211 (69.6%)
	3	68 (22.4%)
Neutrophil : lymphocyte ratio, median (range)		2.58 (0.50–17.25)
Preoperative albumin, g/dl, median (range)		44 (26–52)
POSSUM physiological score, median (range)		16 (12–32)
Operation, *n* (%)	Right hemihepatectomy	129 (42.6%)
	Extended right	13 (4.3%)
	Left hemihepatectomy	35 (11.6%)
	Extended left	3 (1.0%)
	Left lateral sectorectomy	31 (10.2%)
	Wedge resection	79 (26.1%)
	Other	13 (4.3%)
RFA included, *n* (%)	Yes	19 (6.3%)
	No	284 (93.7%)
Wedge resection included, *n* (%)	Yes	122 (40.3%)
	No	181 (59.7%)
Number of segments resected, median (range)		4 (1–6)
Repeat operation, *n* (%)	Yes	33 (10.9%)
	No	270 (89.1%)
Curative resection, *n* (%)	Yes	284 (93.7%)
	No	19 (6.3%)
Number of tumours, median (range)		1 (1–10)
Maximum tumour diameter, mm, median (range)		35 (3–155)
Resection margin, *n* (%)	R0	232 (76.6%)
	R1	71 (23.4%)

MRI, magnetic resonance imaging; PET, positron emission tomography; BMI, body mass index; ASA, American Society of Anesthesiologists; RFA, radiofrequency ablation.

Table 2 Distribution of population categorized by socioeconomic status in the UK, and in Devon and Cornwall, and in those undergoing liver resection for colorectal liver metastases. Socioeconomic status was unclassified for eight patients. (Comparison between the proportion of residents of Devon and Cornwall and those undergoing liver resection: $P < 0.001$)

Deprivation category	UK residents, *n* (%)	Residents of Devon and Cornwall, *n* (%)	Patients undergoing liver resection, *n* (%)
1 Wealthy achievers (least deprived)	14 967 871 (24.8%)	580 065 (34.6%)	137 (46.4%)
2 Urban prosperous	7 594 891 (12.6%)	93 708 (5.6%)	11 (3.7%)
3 Comfortably off	16 656 466 (27.6%)	497 182 (29.7%)	93 (31.5%)
4 Moderate means	8 449 324 (14.0%)	271 357 (16.2%)	31 (10.5%)
5 Hard-pressed (most deprived)	12 715 861 (21.1%)	232 757 (13.9%)	23 (7.8%)
Total	60 384 413	1 676 069	295

0.21–7.36 years) in the most deprived categories ($P = 0.511$). The median number of surveillance scans performed was three (range: one to nine) in both the least and most deprived groups ($P = 0.938$). Tumour recurrence occurred in 163 patients; there was no difference in recurrence rate [77/133 (57.9%) versus 30/50 (60.0%); $P = 0.867$] or median time to recurrence between patients in the two least deprived (0.56 years; range: 0.14–2.74 years) and two most deprived (0.61 years; range: 0.21–3.91 years) categories ($P = 0.305$). There was no difference among the disease-free survival curves for each category of SES ($P = 0.913$) (Fig. 1).

Among those patients who underwent planned curative resections and for whom socioeconomic data were available, including those in whom no surveillance imaging was performed ($n = 277$), there were a total of 96 deaths during the study period (34.7%). There was no significant difference in mortality rate between patients in the two least deprived categories (42/136, 30.9%) and those in the two most deprived categories (18/53, 34.0%) ($P = 0.729$). Twelve patients died within 90 days of surgery (4.3%), but there was no significant difference in 90-day mortality between patients in the two least deprived (4/136, 2.9%) and those in the two most deprived (3/53, 5.7%) categories ($P = 0.403$). There was no difference in overall survival curves across categories of SES ($P = 0.190$) (Fig. 2).

Multivariate analysis of factors potentially associated with tumour recurrence (Table 4) demonstrated no association between SES and tumour recurrence ($P = 0.700$). Only the number of liver metastases ($P = 0.014$) and maximum tumour diameter ($P = 0.001$) were associated with tumour recurrence. Each additional liver metastasis increased the risk for recurrence by a factor of 1.28, and each additional millimetre in tumour diameter had a small effect, increasing the risk for recurrence by a factor of 1.02.

Discussion

The principal finding of this study is that the SES of patients undergoing liver resection for CLM is not representative of that of the local population because the proportion of patients from the least deprived categories is higher than expected and that of patients from the most deprived categories is lower than expected. Amongst patients undergoing liver resection for CLM, the degree of socioeconomic deprivation had no effect on tumour recurrence after resection.

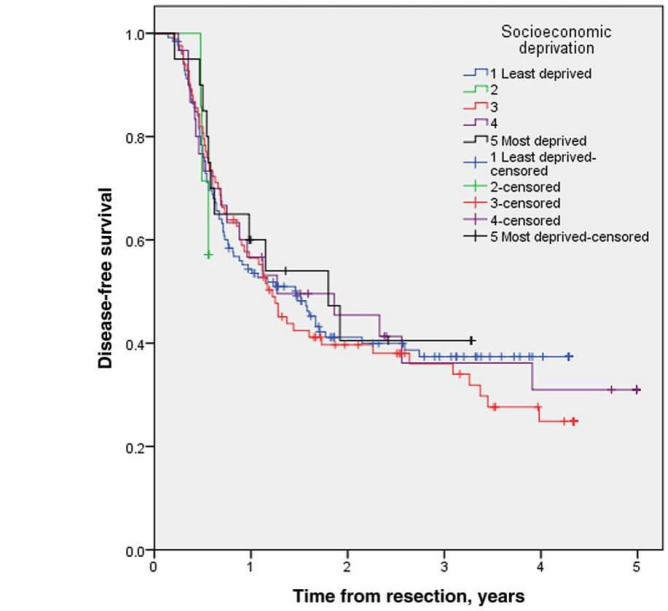
The finding that people from the least deprived categories of SES account for a higher proportion of patients undergoing liver surgery for CLM than they do in the local population is significant and in keeping with the present authors' clinical observations. The comparison is subject to bias as the incidence of colorectal cancer is influenced by SES and the disease is more common in populations with greater levels of deprivation.[1] This would tend therefore to increase the differences observed in the proportions of the different population categories submitted to liver surgery in comparison with those within the local population because CLM would be expected to occur more commonly amongst patients of lower SES. There are many potential reasons why patients with the least deprivation are more likely to undergo surgery for CLM, despite being at lower risk for the development of colorectal cancer. Patients with higher levels of deprivation are more likely to suffer postoperative complications and death following primary colorectal cancer surgery[16] and are likely to have more or more severe comorbidities that render them unfit for further surgery. Socioeconomic status is associated with educational attainment,[17] and patients with greater deprivation may be less aware of the potential benefits of treatment for metastatic disease. This may affect patients' willingness to engage with longterm surveillance to detect metachronous disease and to seek referral to an HPB unit. There is also an element of discretion by clinical practitioners in many stages of the patient pathway prior to surgery for CLM, which may be influenced by perceptions of degree of socioeconomic deprivation.

Interestingly, there was a large disparity in the use of staging PET scans, which were performed in 74.5% of patients from the least deprived groups compared with only 30.4% of patients from the most deprived. This may be partly explained by the higher incidence of T4 primary tumours amongst the least deprived patients, which is one of the indications for PET scans in national guidelines,[6] but is not otherwise explicable by the other measures of disease burden used in this study.

Table 3 Preoperative and operative characteristics of the 148 least (categories 1 and 2) and 54 most (categories 4 and 5) socioeconomically deprived patients undergoing liver resection for colorectal liver metastases

		Least deprived patients	Most deprived patients	
		Categories 1 + 2 (n = 148)	Categories 4 + 5 (n = 54)	P-value
Age, years, median (range)		67 (34–88)	67 (33–90)	0.562
Gender, n (%)	Female	56 (37.8%)	23 (42.6%)	0.625
	Male	92 (62.2%)	31 (57.4%)	
T stage of primary, n (%)	0	2 (1.4%)	0	0.060
	1	4 (2.7%)	1 (1.9%)	
	2	12 (8.1%)	2 (3.7%)	
	3	71 (48.0%)	39 (72.2%)	
	4	52 (35.1%)	11 (20.4%)	
	Unavailable	7 (4.7%)	1 (1.9%)	
N stage of primary, n (%)	0	64 (43.2%)	24 (44.4%)	0.781
	1	50 (33.7%)	16 (29.6%)	
	2	30 (20.3%)	13 (24.1%)	
	Unavailable	4 (2.7%)	1 (1.9%)	
Site of primary, n (%)	Colonic	77 (52.0%)	29 (53.7%)	0.874
	Rectal	71 (48.0%)	25 (46.3%)	
Timing	Synchronous	71 (48.0%)	21 (38.9%)	0.268
	Metachronous	77 (52.0%)	33 (61.1%)	
Preoperative MRI, n (%)	Yes	83 (56.1%)	29 (53.7%)	0.873
	No	65 (43.9%)	25 (46.3%)	
Preoperative PET, n (%)	Yes	111 (75.0%)	25 (46.3%)	<0.001
	No	37 (25.0%)	29 (53.7%)	
Preoperative liver-directed chemotherapy, n (%)	Yes	77 (52.0%)	25 (46.3%)	0.526
	No	71 (48.0%)	29 (53.7%)	
Preoperative diabetes, n (%)	Yes	16 (10.8%)	3 (5.6%)	0.413
	No	132 (89.2%)	51 (94.4%)	
BMI, kg/m^2, median (range)		27 (17–39)	27 (19–54)	0.859
ASA class, n (%)	1	16 (10.8%)	1 (1.9%)	0.030
	2	104 (70.3%)	36 (66.7%)	
	3	28 (18.9%)	17 (31.5%)	
Neutrophil : lymphocyte ratio, median (range)		2.38 (0.50–10.10)	2.85 (0.94–17.25)	0.161
Preoperative albumin, g/dl, median (range)		44 (29–51)	43 (34–51)	0.102
POSSUM physiological score, median (range)		16 (12–32)	17 (13–30)	0.720
RFA included, n (%)	Yes	11 (7.4%)	4 (7.4%)	1.000
	No	137 (92.6%)	50 (92.6%)	
Wedge resection included, n (%)	Yes	68 (45.9%)	21 (38.9%)	0.425
	No	80 (54.1%)	33 (61.1%)	
Number of segments resected, median (range)		4 (1–6)	3 (1–6)	0.617
Repeat operation, n (%)	Yes	15 (10.1%)	4 (7.4%)	0.786
	No	133 (89.9%)	50 (92.6%)	
Curative resection, n (%)	Yes	136 (91.9%)	53 (98.1%)	0.191
	No	12 (8.1%)	1 (1.9%)	
Number of liver metastases, median (range)		2 (1–10)	1 (1–8)	0.317
Maximum diameter of metastases, mm, median (range)		30 (3–120)	35 (5–120)	0.063
Resection margin, n (%)	R0	115 (77.7%)	44 (81.5%)	0.698
	R1	33 (22.3%)	10 (18.5%)	

MRI, magnetic resonance imaging; PET, positron emission tomography; BMI, body mass index; ASA, American Society of Anesthesiologists; RFA, radiofrequency ablation.

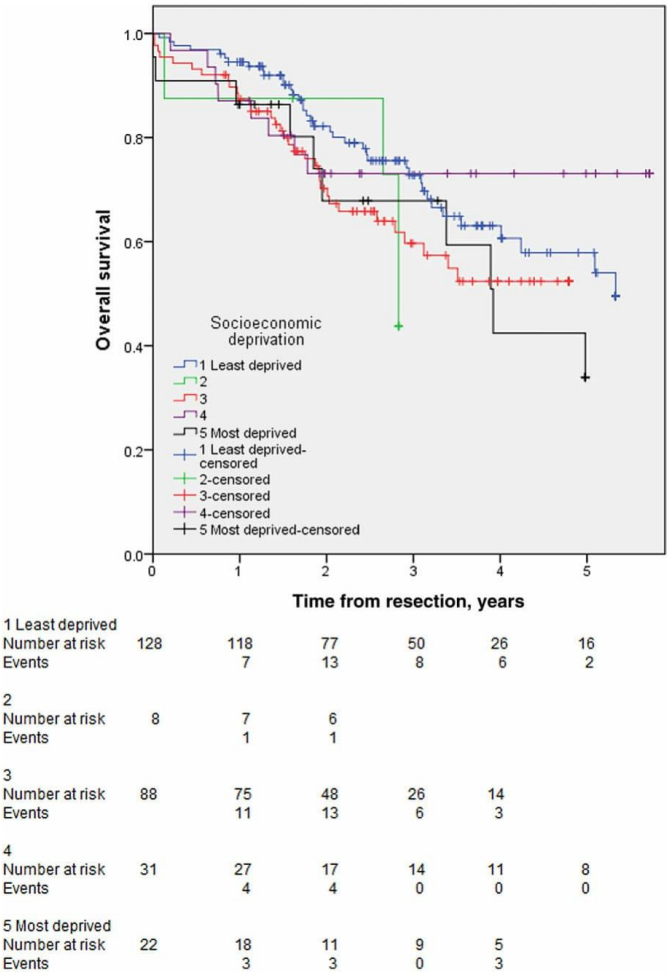


1 Least deprived					
Number at risk	126	66	35	26	13
Events		57	14	3	0
2					
Number at risk	7				
Events		3			
3					
Number at risk	83	46	25	18	9
Events		36	13	2	5
4					
Number at risk	30	17	11	7	6
Events		13	3	2	1
5 Most deprived					
Number at risk	20	11	6	5	
Events		8	3	0	

Figure 1 Kaplan–Meier curves for disease-free survival in 303 patients with colorectal liver metastases submitted to liver resection stratified according to socioeconomic status. Categories 1–5 represent, respectively: wealthy achievers; the urban prosperous; the comfortably off; those of moderate means, and the hard-pressed

There was no difference in objective measures of health between patients in the highest and lowest categories of SES, as shown by the presence of preoperative diabetes, physiological score or body mass index. This may reflect the greater selection of patients from more deprived groups, in whom the rate of these markers of poor health might be expected to be higher. There was, however, a small difference in subjective measures of health as determined by ASA grade.

To categorize SES, this study used the ACORN® system, which has been used in a number of epidemiological studies.[18–21] This system has advantages in that economic data are drawn from a wide range of sources in addition to property values. Other studies addressing the influence of SES on health care outcomes have used the income domain of the Index of Multiple Deprivation (IMD) score[22] and the Townsend index.[23] These systems have been used simultaneously in previous studies[24,25] and neither method has



1 Least deprived						
Number at risk	128	118	77	50	26	16
Events		7	13	8	6	2
2						
Number at risk	8	7	6			
Events		1	1			
3						
Number at risk	88	75	48	26	14	
Events		11	13	6	3	
4						
Number at risk	31	27	17	14	11	8
Events		4	4	0	0	0
5 Most deprived						
Number at risk	22	18	11	9	5	
Events		3	3	0	3	

Figure 2 Kaplan–Meier curves for overall survival in 303 patients with colorectal liver metastases submitted to liver resection stratified according to socioeconomic status. Categories 1–5 represent, respectively: wealthy achievers; the urban prosperous; the comfortably off; those of moderate means, and the hard-pressed

been shown to be superior. Moreover, the difficulties of analysing and interpreting socioeconomic data have been described.[26] However, the systems allow for the valid and simultaneous comparison of different populations in contexts in which potential bias and inaccuracy will affect the populations under study equally.

In a manner reflecting the findings of previous work,[8] degree of socioeconomic deprivation was not shown to be associated with either 90-day mortality or disease recurrence. The most likely explanation for this to be derived from the present data is not that SES does not affect these outcomes, but that greater selection occurs amongst patients of lower SES to favour patients who are likely to have better outcomes.

The difference in the rates of liver resection for CLM according to SES may reflect selection on the basis of objective health measures. However, further study is required to confirm this and to

Table 4 Univariate and multivariate analyses of factors associated with tumour recurrence following liver resection for colorectal liver metastases in 266 patients

		Univariate analysis				Multivariate analysis		
		Not recurred (*n* = 103)	Recurred (*n* = 163)	*P*-value	Odds ratio (95% CI)	*P*-value		Odds ratio (95% CI)
Age[a], years, median (range)		65 (36–88)	67 (33–87)	0.872				
Gender, *n* (%)	Male	67 (65.0%)	105 (64.4%)	0.863				
	Female	36 (35.0%)	58 (35.6%)					
SES category, *n* (%)	1 (least deprived)	52 (50.5%)	74 (45.4%)	0.700				
	2	4 (3.9%)	3 (1.8%)					
	3	27 (26.2%)	56 (34.4%)					
	4	11 (10.7%)	19 (11.7%)					
	5 (most deprived)	9 (8.7%)	11 (6.7%)					
T stage of primary, *n* (%)	0, 1 or 2	10 (9.7%)	18 (11.0%)	0.147[b]		0, 1, 2 versus 3	0.504	0.79 (0.40–1.56)
	3	61 (59.2%)	93 (57.1%)			3 versus 4	0.706	1.11 (0.68–1.80)
	4	29 (28.2%)	47 (28.8%)					
N stage of primary, *n* (%)	0	50 (48.5%)	67 (41.1%)	0.828				
	1	34 (33.0%)	53 (32.5%)					
	2	18 (17.5%)	40 (24.5%)					
Site of primary colorectal tumour, *n* (%)	Colon	55 (53.4%)	75 (46.0%)	0.389				
	Rectum	48 (46.6%)	88 (54.0%)					
Timing, *n* (%)	Synchronous	46 (44.7%)	78 (47.9%)	0.584				
	Metachronous	57 (55.3%)	85 (52.1%)					
Preoperative chemotherapy, *n* (%)		47 (45.6%)	85 (52.1%)	0.412				
Preoperative diabetes, *n* (%)		7 (6.8%)	15 (9.2%)	0.523				
BMI, kg/m^{2}[a], median (range)		27 (19–54)	27 (16–50)	0.518				
ASA class, median (range)		2 (1–3)	2 (1–3)	0.566				
Preoperative albumin, g/dl[a], median (range)		44 (34–50)	44 (26–52)	0.949				
POSSUM physiological score[a], median (range)		17 (12–32)	16 (12–32)	0.378				
Neutrophil : lymphocyte ratio (preop)[a], median (range)		2.4 (0.5–17.3)	2.6 (0.7–9.1)	0.211[b]	1.09 (0.95–1.26)	0.079		1.09 (0.94–1.28)
Preoperative MRI, *n* (%)		59 (57.3%)	87 (53.4%)	0.640				
Preoperative PET, *n* (%)		68 (66.0%)	110 (67.5%)	0.930				
Wedge resection included, *n* (%)		31 (30.1%)	67 (41.1%)	0.117[b]		0.062		1.70 (0.98–2.94)
RFA included, *n* (%)		6 (5.8%)	10 (6.1%)	0.959				
Number of segments resected[a], median (range)		4 (1–6)	4 (1–6)	0.222[b]	1.10 (0.94–1.28)	0.120		1.00 (0.94–1.07)
Repeat operation, *n* (%)		11 (10.7%)	18 (11.0%)	0.105[b]		0.824		1.04 (0.39–2.77)
Number of tumours[a], median (range)		1 (1–7)	2 (1–10)	0.007[b]	1.29 (1.07–1.55)	0.014		1.28 (1.06–1.56)
Largest tumour diameter, mm[a], median (range)		28 (3–155)	35 (6–150)	0.002[b]	1.02 (1.01–1.03)	0.001		1.02 (1.00–1.04)
Resection margin <1 mm (R1), *n* (%)		18 (17.5%)	45 (21.2%)	0.212[b]		0.372		1.03 (0.94–1.07)

[a]In univariate analysis continuous variables were tested with logistic regression. Categorical variables were tested with the chi-squared test.
[b]Significant at the level of <0.25 for univariate analysis and tested in multivariate analysis.
95% CI, 95% confidence interval; SES, socioeconomic status; BMI, body mass index; ASA, American Society of Anesthesiologists; MRI, magnetic resonance imaging; PET, positron emission tomography; RFA, radiofrequency ablation.

ensure equity of access to specialized hepatobiliary services within a publicly funded health care system. Similar differences may be found in other countries, especially those with systems of predominantly private health insurance, and the selection of patients for surgery on the basis of SES may influence the comparison of outcomes between countries.

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Conflicts of interest

None declared.

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